

021342 - 5004 P1P

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

21-342/S-004

Trade Name: Levo-T Tablets

Generic Name(s): (levothyroxine sodium)

Sponsor: Alara Pharmaceuticals, Inc.

Agent:

Approval Date: June 23, 2004

Indication: Demonstrates bioequivalence between Levo-T and Synthroid in order to obtain an AB rating.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-342-S-004

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-342/S-004

Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-342/S-004

Alara Pharmaceuticals, Inc.
Attention: Mayra Garcia
Senior Regulatory Affairs Associate
P.O. Box 7439
Caguas, Puerto Rico 00726

Dear Ms. Garcia:

Please refer to your supplemental new drug application dated June 11, 2003, received June 12, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levo-T (levothyroxine sodium tablets, USP).

We acknowledge receipt of your submissions dated November 24, 2003, and January 16 and March 18, 2004.

This supplemental new drug application proposes to demonstrate bioequivalence between Levo-T and Synthroid in order to obtain an AB rating.

We have determined your Levo-T (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets to be bioequivalent and therapeutically equivalent to the listed drug Synthroid (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets.

Our review concludes that the data establish bioequivalence between these products, and this supplement is approved. However, your supplement requested an "AB" rating for interchangeability between Levo-T and Synthroid. That decision will be made by the Office of Generic Drugs, and any change in the rating of this product will be listed in the next monthly supplement to the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book") published by the Agency.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 21-342/S-004

Page 2


If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Project Manager, at (301) 827-6381.

Sincerely,


{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

David Orloff
6/23/04 04:38:17 PM

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-342/S-004

Medical Review(s)

MEMO TO FILE

NDA: 21-210/SE4
Sponsor: Jerome Stevens Pharmaceuticals
Drug Name: Unithroid
Date of Submission: February 13, 2004
Subject: Review of Financial Disclosure Information

In compliance with 21 CFR 54.2, the sponsor has submitted financial disclosure information for all clinical investigators participating in clinical studies whose results are relied upon for the approval of this supplement.

I have reviewed the documents submitted and all investigators have provided statements denying the following:

- entering into any financial arrangements with the sponsor of the clinical trial
- receiving significant payments of other sorts
- holding proprietary interest in the tested product
- having significant equity interest in the sponsor of the clinical trial

The sponsor has provided sufficient information for this reviewer to conclude that there are no financial conflicts of interest on the part of the investigator(s) to question the integrity of the data submitted.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Mary Parks
6/15/04 01:01:32 PM
MEDICAL OFFICER

Levo-T™ (Levothyroxine Sodium Tablets, USP)

NDA 21-342

ALARA Pharmaceutical Corporation

Prior Approval Supplement

BIOAVAILABILITY/BIOEQUIVALENCE

B. Financial Certification/Disclosure Statement

Completed FDA Form 3454 Certification: Financial Interests and Arrangements of Clinical Investigators is provided with the corresponding attachment.

We are also including Financial Disclosures signed by the Clinical Investigators at [] who participated in Project AA03790.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: June 30, 2002

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

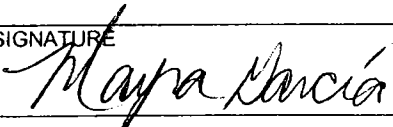
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Mayra García	TITLE Sr. Reg. Affairs Associate
FIRM / ORGANIZATION ALARA Pharmaceutical Corporation	
SIGNATURE 	DATE 6/11/03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Levo-T™ (Levothyroxine Sodium Tablets, USP)
NDA 21-342
ALARA Pharmaceutical Corporation
Prior Approval Supplement

ATTACHMENT TO FORM FDA 3454

CLINICAL INVESTIGATORS

14

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page(s) of trade secret.

and/or confidential

commercial information

(b4)

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-342/S-004

**Clinical Pharmacology and Biopharmaceutics
Review**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-342
 Submission Date(s): 11-June-2003, 11-November-2003
 Brand Name Levo-T™
 Generic Name Levothyroxine sodium tablets, USP
 Reviewer Sang M. Chung, Ph.D.
 Team Leader Hae-Young Ahn, Ph.D.
 OCPB Division DPE-2
 OND division Metabolic and Endocrine (HFD-510)
 Sponsor ALARA Pharmaceuticals, Cop.
 Submission Type Supplement (S-004) for AB rating
 Strength(s) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets
 Indication Hypothyroidism and suppression of thyroid-stimulating hormone

1 Executive Summary

The sponsor submitted this supplement to demonstrate interchangeability for Levo-T™ (test) with Synthroid® (reference) manufactured by Abbott Laboratories (table 1). The tablet of 0.3mg Synthroid® has been listed as one of reference listed drugs in the Electronic Orange Book as of July 2003.

Table 1 Information on test and reference products

	Test	Reference
Name	Levo-T™ 0.3 mg tablet	Synthroid® 0.3 mg tablet
Lot No.	HT4691	0000341461
Manufactured Date	December 08, 2002	
Exp. Date		November 01, 2003
Assay*	99.2%	99.5%
Content Uniformity* (mean of 10 tablets)	98.7% (range 98.1% - 99.3%)	99.8% (range 99.5% - 100.1%)

*: Specification was 98.1% and 99.5% for the assay and the content uniformity (each tablet), respectively.

A comparative bioavailability between two formulations was assessed in an open-label, single dose, crossover study in healthy volunteers (Protocol AA01991). Oral doses of 0.6mg (two 0.3mg tablets) were administered under overnight fasting condition.

Total of 14 blood samples were collected at Day 0 (1 day before the dosing) for baseline adjustment (i.e., at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 hour, and 5 minute before the dose as 24 hour matching baseline time point). In addition, total of 15 blood samples were collected for levothyroxine PK characterization after the dosing (i.e., 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 48, and 72 hours post-dose). The pre-dose concentration-time profiles (i.e., Day 0) were regarded as the baselines. The post-dose concentration-time profiles were adjusted by the baselines using matching time point subtraction of pre-dose levels from the post-dose levels up to 16 hours post-dose. Negative values after the correction were set to zero. There was 35 days washout period between the treatment periods. Ratios of AUCs (i.e., AUC_{0-24} , AUC_{0-48} , and AUC_{0-72}) and C_{max} (test/reference), and 90% confidence interval (CI) were calculated with the adjusted serum concentrations based on the current recommendation on statistical methods in Guidance for Industry**.

**: 1. Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations.

2. Guidance for Industry; Levothyroxine sodium tablets – *In vivo* pharmacokinetic and bioavailability studies and *in vitro* dissolution testing

Among 27 subjects enrolled for the study, 24 subjects completed the study and statistical analyses were performed using the pharmacokinetic data from the 24 subjects. Three subjects were excluded in the statistical analyses because 2 subjects withdrew consent after the first treatment and 1 subject missed blood collection at the 48 and 72 hour after the second treatment.

Concentration-time profiles are shown in the figure 1.

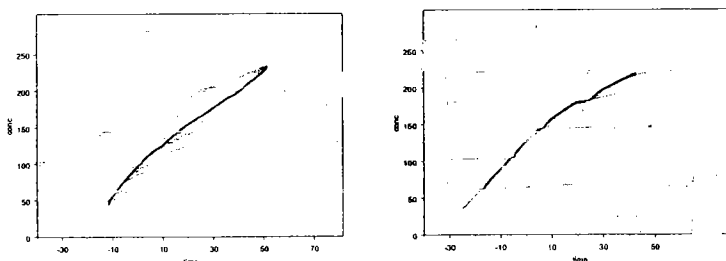


Figure 1

Concentration-time profiles by the periods (left panel) and the treatment effect (right panel). Left panel: solid line for period 1 and broken line for period 2, right panel: solid line for the test product (Levo-T[®]) and broken line for the reference (Synthroid[®]).

The sponsor was asked to adjust the baseline using the current FDA method (i.e., using average of 3 points) and the results of re-analyses were submitted on 24-NOV-2003. The *in vivo* study results using the both methods (i.e., current FDA method and the sponsor's original method) met the current statistical criteria for the BE between the test (Levo-T™) and the reference (Synthroid®) formulations as summarized in Table 2.

Table 2 Statistical results for BE assessment based on the baseline corrected data (mean ratio of test/reference (90% confidence interval))

Parameter	Current FDA method	Sponsor's method
AUC ₀₋₂₄	111.3 (103.5-119.6)	112.2 (105.9-119.0)
AUC ₀₋₄₈	112.5 (103.3-122.5)	113.6 (105.7-122.1)
AUC ₀₋₇₂	109.7 (100.8-119.4)	110.8 (102.9-119.3)
C _{max}	107.9 (100.9-115.4)	105.9 (99.2-113.0)

The serum total levothyroxine (T4) was analyzed using the LC-MS/MS with a validated range of $0.1 - 100$ ng/ml. Three nominal concentrations for QC were 0.1 (LQC), 1 (MQC), and 10 (HQC) ng/ml. Between-batch accuracy (%nominal) and precision (%CV) are summarized in Table 3.

Table 3 Between-batch precision and accuracy from 11 QC samples

QC (ng/ml)	LQC	MQC	HQC
% nominal	100	100	100
% CV	8.1	4.1	6.7

In addition, the sponsor requested a waiver of *in vivo* bioequivalence (BE) studies for the 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 microgram strengths by referencing for dosage form equivalence and comparative dissolution data. The review of the original NDA concluded that dosage form equivalence was established among 50, 100, and 300 microgram strengths and dissolution profiles were comparable among all the strengths with proportionality in its active and inactive ingredients. In conclusion, the request of bio-waiver can be granted.

The sponsor conducted a comparative dissolution test between the test and the reference product. However, similarity calculations (f_2) per strength for the sameness can not be calculated based on the data (table 4) because of fast dissolution; dissolution of test and reference products showed more than or equal to 0.75 at 15 minute except 137mcg of Synthroid®.

Table 4

In-Vitro Dissolution data comparison (mean of 12 tablets)

Time (min)	Test				Reference				
	5	10	15	20	5	15	30	45	60
25mcg	79	87	89	87	64	103	107	108	108
50mcg	91	94	94	94	54	91	95	96	96
75mcg	77	82	85	85	50	87	92	93	92
88mcg	87	92	93	93	56	90	96	97	96
100mcg	92	98	98	96	48	85	92	93	94
112mcg	84	91	94	95	50	85	89	89	90
125mcg	86	91	97	98	57	89	96	96	97
137mcg	88	94	95	96	38	73	86	91	92
150mcg	89	95	97	96	52	87	96	97	97
175mcg	87	94	100	100	51	87	93	93	95
200mcg	83	91	95	95	58	85	91	93	94
300mcg	82	94	98	99	49	79	84	88	90

Dissolution conditions were USP apparatus II (paddle) at 50 rpm in 500 ml of 0.01 N HCl containing 0.2% sodium lauryl sulfate. Dissolution specification was that NLT 80% (Q=80%) of levothyroxine sodium was dissolved in 15 minutes for Levo-T and NLT 70% (Q=70%) in 45 minutes for Synthroid.

The Division of Scientific Investigations (DSI) conducted audits of clinical study site and analytical study site, and recommended accepting the data from the study. The transmittal memo from DSI is in the attachment 2. According to the final report, there was an error in the adjusted concentration of 72 hour for 3 subjects at period 1. However, the recalculation did not affect the study outcome.

Optional Inter-Division CPB briefing was held on 28-APR-2004 at 13B45 (Attendee: Drs. Henry Malinowski, Dale Conner, Barbara Davit, Stella Machado, Don Schuirmann, Solomon Sobel, Kati Johnson, Hae-Young Ahn and Sang M. Chung) and it was concluded that the results were acceptable.

Studies were conducted at the following facilities:

- Clinical study
 - L
- Analytical study and statistical analysis
 - L

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-2) reviewed the supplemental NDA 21-342 S004 and finds it acceptable. This recommendation should be sent to the sponsor as appropriate.

List of Attachments

1. Synopsis
2. DSI report

Attachment starts here.

1. Synopsis

08

LEVOTHYROXINE 300 MCG TABLETS
FINAL REPORT

REPORT NO. AA03790

V. STUDY SYNOPSIS

- Title:** Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of MOVA Pharmaceutical (Levo-T™) and Abbott Laboratories (Synthroid®) 300 mcg Levothyroxine Sodium Tablets in Healthy Adult Volunteers under Fasting Conditions Following Administration of a 600 mcg Dose.
- Objective:** The objective of this study was to compare the single-dose relative bioavailability of MOVA Pharmaceutical (Levo-T™) and Abbott Laboratories (Synthroid®) 300 mcg levothyroxine sodium tablets in healthy adult volunteers under fasting conditions following administration of a 600 mcg dose.
- Study Design:** This was an open-label, randomized, single-dose, 2-way crossover, relative bioavailability study performed on 24 healthy adult volunteers and 4 alternates (19 males and 9 females). A total of 26 subjects (17 males and 9 females) completed the clinical phase of the study. In each period, subjects were housed from at least 36 hours before dosing until after the 24-hour blood draw. Subjects returned for all subsequent blood draws. There was a 35-day washout period between Period 1 and 2 dosing.
- Methods:** The AUC 0-72, AUC 0-48, AUC 0-24, Cmax and tmax pharmacokinetic parameters were calculated for baseline-adjusted and unadjusted serum levothyroxine (Total T4). Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were performed on the ln-transformed baseline-adjusted pharmacokinetic parameters AUC 0-24, AUC 0-48, AUC 0-72 and Cmax. As secondary analysis, ANOVA were performed on the ln-transformed unadjusted pharmacokinetic parameters AUC 0-24, AUC 0-48, AUC 0-72 and Cmax. The ANOVA and ANCOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. The ANCOVA was performed using the ln-transformed pre-dose corresponding area under the curve as covariate for adjusted AUC 0-24, AUC 0-48 and AUC 0-72 and the ln-transformed pre-dose concentration corresponding to the time of the baseline adjusted Cmax as covariate for adjusted Cmax. The ratios of means were calculated using the exponentiation of the least-squares means (LSM) from the analyses on the ln-transformed baseline-adjusted and unadjusted pharmacokinetic parameters AUC 0-24, AUC 0-48, AUC 0-72 and Cmax.

Results: The pharmacokinetic results for total T4 in serum are listed below.

Ratios of LSM (90% Confidence Intervals)
Baseline-Adjusted
(ANOVA)

Parameter	MOVA (A) vs Abbott (B)
AUC 0-24	112.2% (105.9% - 119.0%)
AUC 0-48	113.6% (105.7% - 122.1%)
AUC 0-72	110.8% (102.9% - 119.3%)
Cmax	105.9% (99.2% - 113.0%)

Ratios of LSM (90% Confidence Intervals)
Baseline-Adjusted
(ANCOVA)

Parameter	MOVA (A) vs Abbott (B)
AUC 0-24	111.8% (105.4% - 118.7%)
AUC 0-48	113.3% (105.3% - 121.8%)
AUC 0-72	110.2% (102.4% - 118.5%)
Cmax	105.7% (98.9% - 113.1%)

Ratios of LSM (90% Confidence Intervals)
Unadjusted
(ANOVA)

Parameter	MOVA (A) vs Abbott (B)
AUC 0-24	103.4% (100.4% - 106.5%)
AUC 0-48	103.8% (100.5% - 107.2%)
AUC 0-72	102.4% (99.4% - 105.4%)
Cmax	103.2% (99.2% - 107.3%)

Conclusions: From the ANOVA and ANCOVA, the ratios of least-squares means and 90% confidence intervals derived from the analyses of the ln-transformed baseline-adjusted pharmacokinetic parameters AUC 0-72 and Cmax for Total T4 in serum were within the 80-125% FDA usual acceptance range.

As secondary analyses, ANOVA were also performed on the ln-transformed unadjusted pharmacokinetic parameters AUC 0-72 and Cmax. Results showed that the ratios of least-squares means and 90% confidence intervals were also within the 80-125% FDA usual acceptance range.

The 90% confidence intervals of the relative mean for AUC 0-24 and AUC 0-48 of the test to reference formulation (baseline-adjusted and unadjusted) were presented for information purposes only.

The bioavailability comparison presented in this report follows the FDA guidance recommendations for levothyroxine².

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commercial information

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-342/S-004

Administrative/Correspondence

EXCLUSIVITY SUMMARY FOR NDA # 21-342 SUPPL # -004

Trade Name: Levo-T Generic Name: levothyroxine sodium tablets, USP

Applicant Name: Alara Pharmaceuticals, Inc. HFD # 510

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1) efficacy supplement?
YES /X/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE4

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 /X/

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.

 This supplement sought an AB rating to Synthroid.

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:

 N/A

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 the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) 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 8.

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.

(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 8:

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /___/

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

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 /___/

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

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"):

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: _____

Signature Oluchi Elekwachi, PharmD, MPH Date 6/15/04
Title: Regulatory Project Manager

Signature of _____ Date _____
Division Director: David G. Orloff

Form OGD-011347 Revised 05/10/2004

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-342 Supplement Type (e.g. SE5): SE4 Supplement Number: -004

Stamp Date: June 12, 2003 Action Date: April 12, 2004

HFD 510 Trade and generic names/dosage form: Levo-T (levothyroxine sodium tablets, USP)

Applicant: Alara Pharmaceuticals, Inc. Therapeutic Class: Thyroid

Indication(s) previously approved: hypothyroidism and suppression of thyroid stimulating hormone

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

Number of indications for this application(s): 2

Indication #1: _____

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

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

Other: _____

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-210
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

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

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA ##-###
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)



ALARA Pharmaceutical Corporation

P.O.Box 7439

Caguas, P.R. 00726

Telephone (787) 746-8500

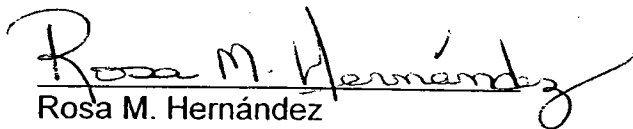
Fax (787) 745-4310

DEBARMENT CERTIFICATION

ALARA Pharmaceutical Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

ALARA Pharmaceutical also certifies, the company has not used any person or affiliate person/firm for whom convictions subject to debarment have occurred in the last five years in any capacity in connection with the development of this product.

If at any time after submission or approval of this application, ALARA Pharmaceutical Corporation becomes aware of any person employed hereby or any affiliate person/firm is in the process of being debarred, ALARA hereby certifies that it will so notify the Food and Drug Administration immediately.



Rosa M. Hernández

President & COO

ALARA Pharmaceutical Corporation

5/29/03
Date

MEMORANDUM

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

DATE: June 18, 2004

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

TO: NDA 21-342/S-004
Levo-T (levothyroxine sodium) tablets
Alara Pharmaceuticals Corporation
Bioequivalence to Synthroid (Abbott)

SUBJECT: sNDA review issues and recommended action

Background

This application was submitted on June 11, 2003, and included the results of a bioequivalence study comparing Levo-T and Synthroid. The sponsor proposed that the results of the study supported bioequivalence of the test and reference products and that an AB rating in the *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)* publication be granted.

Biopharmaceutics

The Office of Clinical Pharmacology and Biopharmaceutics review is included in the action package. The results of the open-label, single-dose, crossover study in healthy volunteers were reviewed and analyzed. This study was conducted according to guidance issued by the Agency. Using either of two separate baseline correction methods, including that currently recommended by the Agency (using an average of 3 pre-dose determinations of serum T4), the data clearly demonstrate bioequivalence of the two products. The analysis of the data for the 24 subjects completing the crossover study shows that the 90% confidence intervals for the ratios of levothyroxine AUC(0-24), AUC(0-48), AUC (0-72) and Cmax for Levo-T to Synthroid are all within the range of 0.8 to 1.25.

The methods validation for the T_4 assay was acceptable, and the request for a waiver of *in vivo* bioequivalence studies for the dosage strengths other than the 0.3 mg tablet formally tested was granted based on dosage form equivalence and dissolution data submitted to the original NDA.

DSI/Data Integrity

DSI conducted audits of the clinical site and of the analytical site found no deficiencies, and recommended that the data be accepted for review.

Financial disclosure

NDA # 21-342/S-004
Drug: Levo-T (LT4, Alara)
Proposal: AB rating to Synthroid
06/22/04

The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

Recommendation

In concurrence with the conclusions of the review by OCPB, the Division will approve this sNDA and recommends the granting of AB rating of Levo-T to Synthroid by the Office of Generic Drugs.

**APPEARS THIS WAY
ON ORIGINAL**

NDA # 21-342/S-004
Drug: Levo-T (LT4, Alara)
Proposal: AB rating to Synthroid
06/22/04

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

/s/

David Orloff
6/22/04 05:45:05 PM
MEDICAL OFFICER

ALARA Pharmaceutical Corporation

P.O. Box 7439
Caguas, P.R. 00726
Telephone (787) 746-8500
Fax (787) 653-8537



ALARA

ORIGINAL
NDA SUPPL AMENDMENT

564-004 (BB)

RECEIVED
MAR 19 2004
FDR/CDER

March 18, 2004

David Orloff, M.D., Director
FDA/CDER/OND/ODE II
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, MD 20857

NDA 21-342/S-004: Levo-T® (Levothyroxine Sodium Tablets, USP)

AMENDMENT TO SUPPLEMENT 004 – BIOPHARMACEUTIC

Dear Dr. Orloff:

This submission provides for corrected data and recalculations for ln AUC 0-72 PK parameter for study AA03790 already provided in our above mentioned supplement.

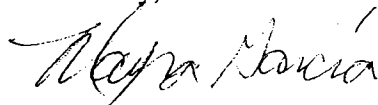
During the FDA Audit to [redacted] [redacted] from February 2 to February 13, 2004, Dr. Nilufer M. Tampa, FDA investigator, noted an error in the baseline corrected concentration value for Subject 11, Period 1, Hour 72. This baseline correction was according to [redacted] [redacted] protocol. [redacted] [redacted] proceeded to review data and proceeded to make the corresponding corrections. The only PK parameter that was affected was ln AUC 0-72. Pharmacokinetic parameters: ln AUC 0-24, ln AUC 0-48, and ln Cmax were unaffected and remained unchanged. The results of the ANOVA and ANCOVA based on the corrected concentration values, the ratios of least-square means for ln AUC 0-72 pharmacokinetic parameter remain within the 80-125% FDA acceptance range. [redacted] [redacted] has responded accordingly to the FDA investigator on February 11, 2004. Included is copy of their response with the corresponding corrected data and recalculations.

This error does not affect results for the values obtained using the baseline correction method requested by the Agency on November 7, 2003 and submitted as an amendment to this supplement on November 24, 2003.

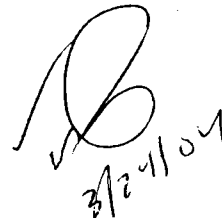
An original and review copy is being provided.

If you should require additional information or assistance, please contact me at (787) 746-8500 Ext. 2119 or by fax (787) 653-8537.

Sincerely,



Mayra García, RAC
Sr. Reg. Affairs Associate



Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT ALARA Pharmaceutical Corporation	DATE OF SUBMISSION March 18, 2004
TELEPHONE NO. (Include Area Code) 787-746-8500	FACSIMILE (FAX) Number (Include Area Code) 787-653-8537
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): P.O. Box 7439 Caguas, PR 00726	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number, if applicable) Not applicable

RECEIVED
MAR 19 2004
FDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-342	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Levothyroxine Sodium; L-3,3',5,5',tetraiodothyronine Sodium Salt	PROPRIETARY NAME (trade name) IF ANY Levo-T®
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Not applicable	CODE NAME (If any) Not Applicable
DOSAGE FORM: Tablet	STRENGTHS: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg
	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

hypothyroidism and Pituitary TSH Suppression

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Amendment S-004 (Biopharmaceutics Information)
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Refer to original application

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Refer to original application

his application contains the following items: (Check all that apply)

- | | |
|-------------------------------------|---|
| <input type="checkbox"/> | 1. Index |
| <input type="checkbox"/> | 2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling |
| <input type="checkbox"/> | 3. Summary (21 CFR 314.50 (c)) |
| <input type="checkbox"/> | 4. Chemistry section |
| <input type="checkbox"/> | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| <input type="checkbox"/> | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| <input type="checkbox"/> | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| <input type="checkbox"/> | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| <input type="checkbox"/> | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) |
| <input type="checkbox"/> | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) |
| <input type="checkbox"/> | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) |
| <input type="checkbox"/> | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) |
| <input type="checkbox"/> | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| <input type="checkbox"/> | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) |
| <input type="checkbox"/> | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) |
| <input type="checkbox"/> | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| <input type="checkbox"/> | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| <input type="checkbox"/> | 15. Establishment description (21 CFR Part 600, if applicable) |
| <input type="checkbox"/> | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| <input type="checkbox"/> | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| <input type="checkbox"/> | 18. User Fee Cover Sheet (Form FDA 3397) |
| <input type="checkbox"/> | 19. Financial Information (21 CFR Part 54) |
| <input checked="" type="checkbox"/> | 20. OTHER (Specify) Corrected Data and PK Parameter Recalculations (AUC 0-72) for Study AA03790 |

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Mayra Garcia</i>	TYPED NAME AND TITLE Mayra Garcia, Sr. Reg. Affairs Associate	DATE: 3/18/04
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 7439 Caguas, Puerto Rico 00726		Telephone Number (787) 746-8500 Ext. 2119

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
DER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Redacted 2

page(s) of trade secret.

and/or confidential

commercial information

(b4)

ORIGINAL ALARA Pharmaceutical Corporation

P.O. Box 7439
Caguas, P.R. 00726
Telephone (787) 746-8500
Fax (787) 745-4310



ALARA

SEW 004 BB

NDA SUPPL AMENDMENT

January 16, 2004

David Orloff, M.D., Director
FDA/CDER/OND/ODE II
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
JAN 20 2004
FDR/CDER

**NDA 21-342/S-004: Levo-T® (Levothyroxine Sodium Tablets, USP)
AMENDMENT TO SUPPLEMENT 004 – BIOPHARMACEUTIC**

Dear Dr. Orloff:

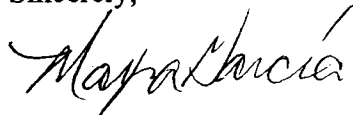
This submission provides for additional data requested by Mr. Sang Chung, Biopharmaceutic Reviewer, in a telephone message on the afternoon of January 12, 2004 for our above mentioned supplement.

We are providing copy of the Validation Report for the Quantitative Determination of Total T-4 (L-Thyroxine) in Human Serum by \square Analytical Method used in the bioequivalency study as requested.

An original and review copy is being provided.

If you should require additional information or assistance, please contact me at (787) 746-8500 Ext. 2119 or by fax (787) 653-8537.

Sincerely,



Mayra García, RAC
Sr. Reg. Affairs Associate

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT ALARA Pharmaceutical Corporation	DATE OF SUBMISSION January 16, 2004
TELEPHONE NO. (Include Area Code) 787-746-8500	FACSIMILE (FAX) Number (Include Area Code) 787-653-8537
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): P.O. Box 7439 Caguas, PR 00726	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Not applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-342		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Levothyroxine Sodium; L-3,3',5,5',tetraiodothyronine Sodium Salt	PROPRIETARY NAME (trade name) IF ANY Levo-T®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Not applicable	CODE NAME (If any) Not Applicable	
DOSAGE FORM: Tablet	STRENGTHS: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

Hypothyroidism and Pituitary TSH Suppression

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION

Amendment S-004 (Biopharmaceutics Information)

PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Refer to original application

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
Refer to original application

This application contains the following items: (Check all that apply)

<input type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Analytical Method Validation Report Requested by Telephone Conversation 1/12/04

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Mayra Garcia</i>	TYPED NAME AND TITLE Mayra Garcia, Sr. Reg. Affairs Associate	DATE: 1/16/04
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 7439 Caguas, Puerto Rico 00726		Telephone Number (787) 746-8500 Ext. 2119

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER (HFD-94) 12229 Wilkins Avenue Rockville, MD 20852
---	--

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

ALARA Pharmaceutical Corporation

P.O. Box 7439

Caguas, P.R. 00726

Telephone (787) 746-8500

Fax (787) 745-4310



ALARA

ORIGINAL

November 24, 2003

RECEIVED

NOV 25 2003

FDR/CDER

David Orloff, M.D., Director
FDA/CDER/OND/ODE II
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, MD 20857

SE4004 (BB)

**NDA 21-342/S-004: Levo-T® (Levothyroxine Sodium Tablets, USP)
AMENDMENT TO SUPPLEMENT 004 – BIOPHARMACEUTICS DATA**

Dear Dr. Orloff:

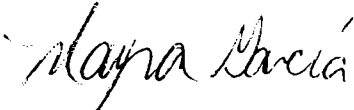
This submission provides for additional data requested by Mr. Sang Chung, Biopharmaceutic Reviewer, in a telephone conversation on the afternoon of November 7, 2003 for our above mentioned supplement.

As requested in the telephone conversation, the data has been recalculated using the correction method requested by the Agency, which required the pre-dose baseline value be calculated as the average of the three concentrations prior to dosing in each period. Also, negative values in the PK data after baseline correction have been recalculated as 0 as requested for S-003.

An original and review copy is being provided.

If you should require additional information or assistance, please contact me at (787) 746-8500 Ext. 2119 or by fax (787) 745-4310.

Sincerely,



Mayra García
Sr. Reg. Affairs Associate

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT ALARA Pharmaceutical Corporation	DATE OF SUBMISSION November 24, 2003
TELEPHONE NO. (Include Area Code) 787-746-8500	FACSIMILE (FAX) Number (Include Area Code) 787-745-4310
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): P.O. Box 7439 Caguas, PR 00726	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Not applicable

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-342		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Levothyroxine Sodium; L-3,3',5,5',tetraiodothyronine Sodium Salt	PROPRIETARY NAME (trade name) IF ANY Levo-T®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) Not applicable	CODE NAME (If any) Not Applicable	
DOSAGE FORM: Tablet	STRENGTHS: 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 137 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:

ypothyroidism and Pituitary TSH Suppression

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO APENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION Amendment S-004 (Biopharmaceutics Data)
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
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<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) <i>Data Recalculation Requested by Telephone Conversation 11/7/03</i>

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

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The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Mayra Garcia</i>	TYPED NAME AND TITLE Mayra Garcia, Sr. Reg. Affairs Associate	DATE: 11/24/03
ADDRESS (Street, City, State, and ZIP Code) P.O. Box 7439 Caguas, Puerto Rico 00726		Telephone Number (787) 746-8500 Ext. 2119

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
JER, HFD-99
401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**SUMMARY OF RESULTS
USING A BASELINE ADJUSTMENT METHOD REQUESTED BY THE FDA**

┌ Project No. AA03790 ┐

STUDY TITLE: COMPARATIVE, RANDOMIZED, SINGLE-DOSE, 2-WAY CROSSOVER BIOAVAILABILITY STUDY OF MOVA PHARMACEUTICAL (LEVO-T™) AND ABBOTT LABORATORIES (SYNTHROID®) 300 MCG LEVOTHYROXINE SODIUM TABLETS IN HEALTHY ADULT VOLUNTEERS UNDER FASTING CONDITIONS FOLLOWING ADMINISTRATION OF A 600 MCG DOSE

DATE: 20/NOV/2003

In the above-mentioned study, the baseline adjustment on serum Total T4 was performed by subtracting the baseline values for each time point from the corresponding post-dose serum concentration time point, with the exception of the 24-, 48- and 72-hour time points. The adjustment for the 24-, 48- and 72-hour time points was performed by subtracting the mean of the Total T4 in serum concentrations obtained at time -24 and -0.083 before dosing. The adjustment was subject, time interval and period specific. Following baseline adjustment, the pre-dose value -0.083 was set to zero for calculation of the pharmacokinetic parameters. Negative concentration values that occurred following the baseline adjustment of serum Total T4 post-dose were included in the calculation of the pharmacokinetic (PK) parameters. This method of adjusting baseline concentrations is the most common and consistent approach ┌ for adjusting plasma, serum, and blood concentrations values to baseline values, as per Global SOP No. GL-PK-10804-00.

However, we have complied with the FDA's request to test an alternate method of baseline adjustment by using the average Total T4 serum concentrations of the three last pre-dose samples (-0.083, -8 and -12 hours pre-dose) for baseline adjustment. In addition, the negative values of adjusted Total T4 serum concentrations were set to zero. The following subject profiles contained negative values for the adjusted Total T4 serum concentrations at the following timepoints:

ID	Period	Time (h)	Adjusted Concentration (ng/mL)
12	1	0.5	┌ ┐
7	2	0.5	┌ ┐
20	2	0.5	┌ ┐

As previously explained, these negative values were set to zero for the purpose of pharmacokinetic and statistical analyses. Statistical outputs are retained on file at ┌

1

**SUMMARY OF RESULTS
USING A BASELINE ADJUSTMENT METHOD REQUESTED BY THE FDA**

[Project No. AA03790]

The pharmacokinetic results are listed below for the baseline adjusted Total T4 in serum:

Mova (A) vs Abbott (B)
Ratios of LSM (A/B)% (90% Confidence Intervals)
(ANOVA)

Parameter	Total T4 – Baseline Adjusted	
	MDS Method	FDA Method
AUC 0-24	112.2%(105.9-119.0%)	111.3% (103.5-119.6%)
AUC 0-48	113.6% (105.7-122.1%)	112.5%(103.3-122.5%)
AUC 0-72	110.8% (102.9-119.3%)	109.7% (100.8-119.4%)
Cmax	105.9% (99.2-113.0%)	107.9% (100.9-115.4%)

Mova (A) vs Abbott (B)
Ratios of LSM (A/B)% (90% Confidence Intervals)
(ANCOVA)

Parameter	Total T4 – Baseline Adjusted	
	MDS Method	FDA Method
AUC 0-24	111.8% (105.4-118.7%)	110.3% (103.0-118.1%)
AUC 0-48	113.3% (105.3-121.8%)	111.1% (102.8-120.1%)
AUC 0-72	110.2% (102.4-118.5%)	108.2% (100.4-116.7%)
Cmax	105.7% (98.9%-113.1%)	108.2% (101.0-116.0%)

The new results for the adjusted serum Total T4 concentrations, presented under the column labelled "FDA method", still meet the standards to determine bioequivalence in this comparative bioavailability study. After correction for baseline using the FDA method, the ratios of least-squares means and 90% confidence intervals derived from the analyses of the ln-transformed pharmacokinetic parameters AUC 0-72 and Cmax for the adjusted Total T4 (from the ANOVA and ANCOVA) were again within the 80-125% FDA acceptance range.

As supportive data, ANOVA and ANCOVA were performed on the ln-transformed pharmacokinetic parameters AUC 0-24 and AUC 0-48 adjusted and unadjusted for baseline. Results show that the ratios of least-squares means and 90% confidence intervals were also within the 80-125% FDA acceptance range.

SUMMARY OF RESULTS
USING A BASELINE ADJUSTMENT METHOD REQUESTED BY THE FDA

[_____] Project No. AA03790

As previously presented in the Final Report for PN AA03790, based on the ANOVA for the unadjusted Total T4, the Mova Pharmaceutical (Levo-T[®]) and Abbott (Synthroid[®]) 300 mcg levothyroxine sodium tablets are bioequivalent under fasting conditions, following a 600 mcg oral dose. The ratios of least-squares means and 90% confidence intervals derived from the analyses of the ln-transformed parameters AUC 0-72 and Cmax for the unadjusted Total T4 were within the 80-125% FDA acceptance range.

**APPEARS THIS WAY
ON ORIGINAL**

**SUMMARY OF RESULTS
USING A BASELINE ADJUSTMENT METHOD REQUESTED BY THE FDA**

[_____] Project No. AA03790

Authentication:

[_____]
[_____]

20/NOV/2003
Date

Authorization:

^ ^ ^
[_____]
[_____]

20/nov/2003
Date

^ ^ ^
[_____]
[_____]

20/Nov/2003
Date

Redacted 4

page(s) of trade secret.

and/or confidential

commercial information

(b4)

10/14/03

NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 21-342 Supplement # 004 SE4

Trade Name: Levo-T
Generic Name: levothyroxine sodium tablets
Strengths: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg

Applicant: Alara Pharmaceuticals

Date of Application: June 11, 2003
Date of Receipt: June 12, 2003
Date clock started after UN: n/a
Date of Filing Meeting: July 10, 2003
Filing Date: August 11, 2003 74-day letter due date: Aug. 25, 2003
Action Goal Date (optional): User Fee Goal Date: April 12, 2004

Change requested: To obtain AB rating between Levo-T and Synthroid

Type of Application: Original (b)(1) NDA _____ Original (b)(2) NDA _____
(b)(1) Supplement yes (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s. Recent analyses indicate this conclusion is not valid. If the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

**This supplement contains all the information needed and does not rely on data in other applications or on literature. Apparently, it is considered to be a 505(b)(1) application.

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S X P _____
Resubmission after a withdrawal? n/a Resubmission after a refuse to file? n/a
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.) n/a

User Fee Status: Paid n/a Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee ID # None

Clinical data? None needed.

YES _____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication?

YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

N/A

YES NO

Is the application affected by the Application Integrity Policy (AIP)?

YES NO

If yes, explain.

If yes, has OC/DMPQ been notified of the submission?

YES N/A NO

• Does the submission contain an accurate comprehensive index? YES NO

• Was form 356h included with an authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? YES NO

If no, explain:

• If an electronic NDA, does it follow the Guidance? YES N/A NO

If an electronic NDA, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

The actual values from the study were submitted as SAS Transport files and lists of variables were submitted in pdf.

Additional comments:

• If in Common Technical Document format, does it follow the guidance? N/A YES NO

• Is it an electronic CTD? N/A YES NO

If an electronic CTD, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

Additional comments:

• Patent information included with authorized signature? YES NO

No patent information submitted for levothyroxine in this supplement. However, the applicant submitted Orange Book information for the comparator, Synthroid.

• Exclusivity requested? YES, _____ years NO

Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge"

• Financial Disclosure information included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

• Field Copy Certification (that it is a true copy of the CMC technical section)? YES N/A NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES
- List referenced IND numbers: **None**
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO
 If yes, distribute minutes before filing meeting.
- **Written guidance on study design and analysis sent to applicant on February 4, 2003.**

Project Management

- Package insert consulted to DDMAC? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? N/A YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

N/A

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

Chemistry

N/A

- Did applicant request categorical exclusion for environmental assessment? YES N/A NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- **Establishment Evaluation Request (EER) submitted to DMPQ?** YES N/A NO
- If parenteral product, consulted to Microbiology Team (HFD-805)? YES N/A NO

If 505(b)(2) application, complete the following section:

Not applicable.

This supplement does not rely for approval on any other application or on literature.

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

YES NO
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

YES NO
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

_____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

_____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

_____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

_____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

_____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

_____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

• Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

• Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

• Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

• Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A YES NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

• A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

• EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

YES, IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

• Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 10, 2003

BACKGROUND: This NDA was approved on March 1, 2002, for treatment of hypothyroidism. This supplement consists of a comparative bioavailability study for Levo-T against Synthroid. The applicant requests an AB rating to Synthroid. The firm implies that it conducted the study and data analysis in accord with the Agency guidance provided in a letter dated February 4, 2003.

ATTENDEES: Sang Chung, Hae-Young Ahn, David Lewis, Mamta Gautam-Basak, Enid Galliers

ASSIGNED REVIEWERS: Sang Chung

<u>Discipline</u>	<u>Reviewer</u>
Medical:	None
Secondary Medical:	None
Statistical:	None
Pharmacology:	None
Statistical Pharmacology:	None
Chemist:	None
Environmental Assessment (if needed):	None
Biopharmaceutical:	Sang Chung
Microbiology, sterility:	None
Microbiology, clinical (for antimicrobial products only):	None
DSI:	Not present
Regulatory Project Manager:	Enid Galliers
Other Consults:	None

Per reviewers, are all parts in English or English translation? YES NO
 If no, explain:

CLINICAL	FILE _____	REFUSE TO FILE _____	<u>N/A</u>
• Clinical site inspection needed:		YES	NO
• Advisory Committee Meeting needed?		YES, date if known _____	<u>NO</u>
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?		<u>N/A</u>	YES NO
CLINICAL MICROBIOLOGY	FILE _____	REFUSE TO FILE _____	<u>N/A</u>
STATISTICS	FILE _____	REFUSE TO FILE _____	<u>N/A</u>

BIOPHARMACEUTICS : If the Synthroid (300 mcg tablets, lot # 0000341461; expiry date 01 Nov 2003) were manufactured according to the approved Synthroid NDA, then the supplement may be filed. This was the conclusion of the filing meeting.

On July 11, 2003, Abbott Labs provided a statement that lot # 0000341461 was manufactured on January 15, 2003. The accompanying certificate of analysis (COA) listed content uniformity values ranging between 101.9 % and 98.4% with an average value of 99.7%. This lot was manufactured after the date of Synthroid's approval () marketed product. Therefore, this supplement may be filed.

FILE X REFUSE TO FILE _____

• Biopharm. inspection needed: YES NO

PHARMACOLOGY FILE _____ REFUSE TO FILE _____ N/A

• GLP inspection needed: YES NO

CHEMISTRY FILE _____ REFUSE TO FILE _____ N/A

• Establishment(s) ready for inspection? YES NO

• Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

X No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS (completed):

1. A "no filing issues" letter was issued to applicant on August 20, 2003 (prior to Day 74).
2. A DSI audit request for [] sites was sent on July 17, 2003. (A complete copy of the supplement was sent to DSI by DMEDP on Sept. 24, 2003.)

{See appended electronic signature page.}

Enid Galliers, Chief, Project Management Staff, HFD-510

C:\File Cabinet\21342\s-004.filing-rev.doc

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

/s/

Enid Galliers
10/14/03 05:12:00 PM
CSO



08.20.03

NO FILING ISSUES IDENTIFIED

NDA 21-342/S-004

Alara Pharmaceutical Corporation
Attention: Mayra Garcia
Sr. Reg. Affairs Associate
P.O. Box 7439
Caguas, Puerto Rico 00726

Dear Ms. Garcia:


Please refer to your June 11, 2003, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levo-T(Levothyroxine Sodium Tablets, USP) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b)(2) of the Act on August 11, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Project Manager, at (301) 827-6381.

Sincerely,


{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug
Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Research and Evaluation

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

/s/

Enid Galliers

8/20/03 05:31:00 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-342	Efficacy Supplement Type SE4	Supplement Number -004
Drug: Levo-T (levothyroxine sodium, USP)		Applicant: Alara Pharmaceuticals
RPM: Oluchi Elekwachi, Pharm.D., M.P.H.		HFD-510 Phone # 301-827-6381
Application Type: <input checked="" type="checkbox"/> 505(b)(1)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		N/A
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		12APR04 (as soon as CP issues) 6/23/0
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input checked="" type="checkbox"/> Other – No Clinical Data
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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 & certifications from foreign applicants are cosigned by US agent.		<input type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.		N/A
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV
• Not Needed		21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	
• 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)	10/14/03
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• 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)	N/A
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	N/A
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	N/A
• 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)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Approval Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	N/A
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	N/A
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	N/A
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	N/A
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	4/29/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	3/8/04
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	N/A
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	N/A
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A () Acceptable () Withhold recommendation
❖ Methods validation	() Completed N/A () Requested () Not yet requested
Nonclinical Pharmacology Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A



DEPARTMENT OF HEALTH & HUMAN SERVICES

ACK 7/1/03

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-342/S-004

PRIOR APPROVAL SUPPLEMENT

ALARA Pharmaceutical Corporation
Attn: Mayra Garcia
Senior Regulatory Affairs Associate
P.O. Box 7439
Caguas, PR 00726

Dear Ms Garcia:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Levo-T™ (levothyroxine sodium tablets, USP)
NDA Number:	21-342
Supplement number:	S-004
Review Priority Classification:	Standard
Date of supplement:	June 11, 2003
Date of receipt:	June 12, 2003

This supplemental application proposes to demonstrate bioequivalence between Levo-T™ (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg and Synthroid® (levothyroxine sodium tablets, USP) with the same strengths, in order to obtain an AB rating in the *Approved Drug Products with Therapeutic Equivalence Evaluations* publication.


Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 11, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 12, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6429.

Sincerely,


{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Enid Galliers
7/1/03 03:56:55 PM

ORIGINAL

ALARA Pharmaceutical Corporation

P.O. Box 7439

Caguas, P.R. 00726

Telephone (787) 746-8500

Fax (787) 745-4310



June 11, 2003

NDA NO. 21342 REF NO. 004
NDA SUPPL FOR SEH

RECEIVED

JUN 12 2003

FDR/CDER

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
FDA/CDER/OND/ODE II
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, MD 20857

PRIOR APPROVAL EFFICACY SUPPLEMENT
NDA 21-342: Levo-T™ (Levothyroxine Sodium Tablets, USP)

Dear Dr. Orloff:

This submission provides for a Prior Approval Efficacy Supplement. ALARA Pharmaceutical Corporation is demonstrating bioequivalence between Levo-T™ (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 and approved Synthroid® (NDA 21-402) (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, in order to obtain an AB rating in the *Approved Drug Products with Therapeutic Equivalence Evaluations* publication.

This supplement is being submitted based on the recommendations provided by the Agency in communication dated February 4, 2003 (copy included).

In order to meet bioequivalence requirements the following *in vivo* study was performed: AA03790 - Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of MOVA Pharmaceutical (Levo-T™) and Abbott Laboratories (Synthroid®) 300 mcg Levothyroxine Sodium Tablets in Healthy Adult Volunteers Under Fasting Conditions Following Administration of a 600 mcg Dose by τ

Also, *in vitro* dissolution profile data for all strengths has been generated.

Chemistry and Manufacturing Controls information regarding the lots used in this bioequivalency supplement have already been provided in NDA 21-342/S-002 (CBE-30 Supplement submitted February 20, 2003).

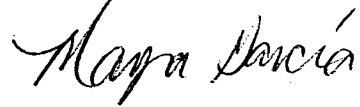
The following criteria has been met in order to classify Levo-T™ therapeutically equivalent to Synthroid®:

- They are approved as safe and effective (Levo-T™ NDA 21-342 approved March 1, 2002 and Synthroid® NDA 21-402 approved July 24, 2002)
- They are pharmaceutical equivalent:
 1. Contain identical amounts of the same active drug ingredient (Levothyroxine Sodium, USP), in the same dosage form (Tablet), and route of administration (Oral)
 2. Meet compendial standards of strength, quality, purity, and identity (Levothyroxine Sodium Tablets, USP)
- They are bioequivalent:
 1. They do not present a known or potential bioequivalence problem
 2. They meet an acceptable *in vitro* standard (USP)
- They are adequately labeled (Labeling template for Levothyroxine Sodium Tablets, USP has been provided by the Agency)
- They are manufactured in compliance with cGMP regulations.

One archival copy and one pharmacokinetics review copy, each of 5 volumes, have been provided.

If you should require additional information or assistance, please contact me at (787) 746-8500 Ext. 2119 or by fax (787) 745-4310.

Sincerely,



Mayra García
Sr. Reg. Affairs Associate
ALARA Pharmaceutical Corporation

Enclosures