

Status of Application for Drug Product Registration

8436

Application Number **8436** Application Complete Application Incomplete Year **2002**

Brand Name **UNITHROID** Dosage Form **Tablet**

Generic Name **Levothyroxine sodium**

Strengths Applied For **25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, 300 mcg**

Classification - **FDA approval pending**

The items below indicate the application's completeness or deficiencies. All deficiencies MUST be addressed prior to final approval by the Council.

Bio-studies Required Bio-studies Provided Biostudy Number **2358**

Bio Studies Reviewed Dissolution Data Required Dissolution Data Submitted

Other Data Required? Other Data Provided Other Data Type(s)

482/483 Provided

Labels Provided

Application Notarized and Legible

NOTES

Application Schedule

NJR Proposal Date	Public Hearing Date	Comments Deadline	DURC Date:	NJR Adopt Date
4/15/2002	5/13/2002	5/20/2002	6/11/2002	7/15/2002

Date application received **3/1/2002**

Application Number **8436**

MFG **Mylan**

New Jersey Department of Health and Senior Services
Drug Utilization Review Council
Room 501, Box 360 Health-Agriculture Building
Market Warren Streets
Trenton, New Jersey 08625-0360

609-292-4029 FAX: 609-292-8713
www.state.nj.us/health/mgmt/drugutil.htm
Robert G. Kowalski, R.Ph.
Acting Executive Director

Friday, March 01, 2002

**New Jersey Department of Health and Senior Services
THE DRUG UTILIZATION REVIEW COUNCIL
Telephone: (609) 292-4029**

8436

Mailing Address:
Drug Utilization Review Council
Room 501
PO Box 360
Trenton, NJ 08625-0360

Overnight Services (UPS, FedEx):
Drug Utilization Review Council
Room 501
369 John Fitch Plaza
Trenton, NJ 08611

**DRUG PRODUCT REGISTRATION
(ONLY MANUFACTURERS MAY APPLY; DISTRIBUTORS ARE NOT TO APPLY)**

New Jersey State Law (N.J.S.A. 24.6E-1 et seq.) created a Drug Utilization Review Council for the purpose of preparing a List of Interchangeable Drug Products ("generic formulary"). The criteria on which acceptable generics are judged are given at N.J.A.C. 8.70. The information requested below, as well as information we may later request, will determine whether your company's products will be listed in the List of Interchangeable Drug Products. Under State Law, any manufacturer may request that a drug product be added to, or removed from, the Formulary.

INSTRUCTIONS:

- Applications must be typewritten and notarized; use this form or an exact copy. **ANSWER ALL QUESTIONS.**
- One application per dosage form. If this is a single ingredient product, several strengths may be listed on one application. Do not submit additional applications for different package sizes.
- If additional space is required, please attach documents and indicate on the application.
- Address applications and questions to the address on the letterhead.
- You must submit a copy of your most recent FDA Form 483. The first page is sufficient.
- You must submit an FDA approval letter, if applicable.
- You must submit copies of your labels that indicate the manufacturer's name.
- If a biostudy is required, submit 2 copies of your biostudy summary with completed Biodata Analysis forms.
- As proof of availability to New Jersey consumers, you must submit a copy of invoices indicating sale to wholesalers or distributors who transact business with New Jersey pharmacies.

1. Name of Manufacturer MYLAN Pharmaceuticals Inc.		2. Date of Application FEB 28 2002	
3. Mailing Address of Manufacturer POB 4310 Morgantown, WV 26505		4. Address of Manufacturing Site (if different)	
5. Name of Contact Person (for clarification of this application) Stephen B. Krinke, RPh		6. Contact's Telephone Number 800.826.9526	
7. Brand for which the above is a substitute: Unithroid®		8. Dosage Form: Tablet	
8. Generic name and strengths of drug submitted for inclusion in the Formulary for single ingredient items OR Name and amount of each active ingredient:			
Levothyroxine Sodium Tablets, USP 25 mcg		Levothyroxine Sodium Tablets, USP 125 mcg	
Levothyroxine Sodium Tablets, USP 50 mcg		Levothyroxine Sodium Tablets, USP 150 mcg	
Levothyroxine Sodium Tablets, USP 75 mcg		Levothyroxine Sodium Tablets, USP 175 mcg	
Levothyroxine Sodium Tablets, USP 88 mcg		Levothyroxine Sodium Tablets, USP 200 mcg	
Levothyroxine Sodium Tablets, USP 100 mcg		Levothyroxine Sodium Tablets, USP 300 mcg	
Levothyroxine Sodium Tablets, USP 112 mcg			

This Application is valid for 1 year from the date published in the New Jersey Register.



MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

March 1, 2002

Robert G. Kowalski, R.Ph.
Acting Executive Director
NJ Drug Utilization Review Council
Market & Warren Streets
CN 360, Room 501
Trenton, NJ 08625-0360

~~8436~~
8436

RECEIVED

MAR -5 2002

Drug Utilization
Review Council

RE: Levothyroxine Sodium Tablets, USP 25, 50, 75, 88, 100, 112, 125, 150,
175, 200 & 300 mcg

Dear Mr. Kowalski:

Enclosed please find an updated "page 2" application page for the recently submitted referenced application. This page contains corrected NDC numbers. Please insert this page into the referenced application.

If you have any questions or need additional information, please do not hesitate to contact me at (800) 796-9526. My fax number is (304) 285-6437.

Thank you for your assistance.

Sincerely,

Eric B. Belldina, R.Ph.
Manager, Government Affairs

0681

Department—Fax Numbers
Accounting
Administration
Business Development
Human Resources

(304) 285-6403
(304) 599-7284
(304) 599-7284
(304) 598-5406

Information Systems
Label Control
Legal Services
Maintenance & Engineering
Medical Unit

(304) 285-6404
(800) 848-0463
(304) 598-5408
(304) 598-5411
(304) 598-5445

Purchasing
Quality Control
Research & Development
Sales & Marketing

(304) 598-5401
(304) 598-5407
(304) 285-6409
(304) 598-3232

DRUG PRODUCT REGISTRATION, CONTINUED

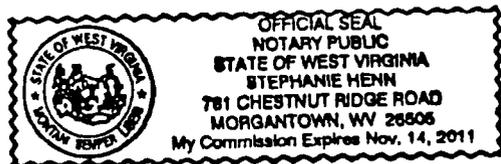
10. Does each batch of this drug conform with official standards prior to being marketed? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	11. Date manufacturing site for this product was last inspected by FDA for CGMP compliance July 16 - 20, 2001												
12. Do you have FDA approval to market this product? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	13. Is this product: Manufactured under an ANDA? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Manufactured under the NDA? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No												
14. Have bioequivalency studies been submitted to the FDA? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No If No, why not?													
15. Has this drug product been involved in any litigation, including patent suits, in the last 2 years? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No (If yes, attach particulars)	16. Does the name of the manufacturer appear on all distributors' labels? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No												
16. Is this product currently available to pharmacies? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No (If yes, attach particulars) If not, when will it be launched? Pending FDA Approval													
17. List four (4) distributors and/or wholesalers who now carry or will carry this product and do business with pharmacies in New Jersey: <table style="width:100%; border-collapse: collapse;"> <tr> <td style="border-bottom: 1px solid black; width: 60%;">McKesson</td> <td style="width: 10%; text-align: center;"><input type="checkbox"/> Now Carry</td> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/> Will Carry</td> </tr> <tr> <td style="border-bottom: 1px solid black;">Bergen Brunswick</td> <td style="text-align: center;"><input type="checkbox"/> Now Carry</td> <td style="text-align: center;"><input checked="" type="checkbox"/> Will Carry</td> </tr> <tr> <td style="border-bottom: 1px solid black;">Kinray</td> <td style="text-align: center;"><input type="checkbox"/> Now Carry</td> <td style="text-align: center;"><input checked="" type="checkbox"/> Will Carry</td> </tr> <tr> <td style="border-bottom: 1px solid black;">H. D. Smith</td> <td style="text-align: center;"><input type="checkbox"/> Now Carry</td> <td style="text-align: center;"><input checked="" type="checkbox"/> Will Carry</td> </tr> </table>		McKesson	<input type="checkbox"/> Now Carry	<input checked="" type="checkbox"/> Will Carry	Bergen Brunswick	<input type="checkbox"/> Now Carry	<input checked="" type="checkbox"/> Will Carry	Kinray	<input type="checkbox"/> Now Carry	<input checked="" type="checkbox"/> Will Carry	H. D. Smith	<input type="checkbox"/> Now Carry	<input checked="" type="checkbox"/> Will Carry
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Kinray	<input type="checkbox"/> Now Carry	<input checked="" type="checkbox"/> Will Carry											
H. D. Smith	<input type="checkbox"/> Now Carry	<input checked="" type="checkbox"/> Will Carry											
19. National Drug Code 00378-1800-01 (25 mcg) 00378-1813-01 (125 mcg) 00378-1803-01 (50 mcg) 00378-1815-01 (150 mcg) 00378-1805-01 (75 mcg) 00378-1817-01 (175 mcg) 00378-1807-01 (88 mcg) 00378-1819-01 (200 mcg) 00378-1809-01 (100 mcg) 00378-1821-01 (300 mcg) 00378-1811-01 (112 mcg)	20. Usual Cost to Pharmacies (AWP/100 or specify) To be determined												
I agree to inform the New Jersey Department of Health and Senior Services in writing of any changes in formulation or product status, manufacturing site, manufacturer name or other information as described herein, within 30 days of such change, and do certify that the information submitted is, to the best of my knowledge, correct and that this product is not now in violation of either Federal or State Law.													

Please notarize individually below:
 Subscribed and sworn to before me this

1st day of March, 2002
Stephanie Henn

[Signature]
 Signature
Director, Trade Relations and Government Affairs
 Title

OC-42
 FEB 01





MYLAN PHARMACEUTICALS INC.

FDA GMP INSPECTION

MYLAN'S LAST GMP INSPECTION OF THE MORGANTOWN, WV FACILITY
WAS CONDUCTED JULY 16-20, 2001.

0683

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		1. DISTRICT OFFICE ADDRESS & PHONE NO 900 Madison Ave. Baltimore, MD 21201 410-962-3396	
2. NAME AND TITLE OF INDIVIDUAL D. Byron Witt Vice-President of Quality Assurance		3. DATE 7-16-01	
4. FIRM NAME Mylan Pharmaceuticals Inc		6. HOUR 11:10 am	8. PHONE # & AREA CODE 304-599-2500
5. NUMBER AND STREET 781 Chestnut Ridge Rd			
7. CITY AND STATE & ZIP CODE Morgantown, WV 26505-4010			

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)]¹ and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264]²

9. SIGNATURE (Food and Drug Administration Employee(s)) William L. Barger David L. Doupnik William G. Warnick	10. TYPE OR PRINT NAME AND TITLE (FDA Employee(s)) William L. Barger - Investigator William A. Warnick - Investigator Dennis L. Doupnik - Investigator
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¹ Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:

Sec. 704 (a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, or restricted devices are manufactured, processed, packed, or held, inspection shall extend to all things therein including records, files, papers, processes, controls, and facilities bearing on whether prescription drugs, nonprescription drugs intended for human use or, restricted devices which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this Act), and research data (other than data relating to new drugs, antibiotic drugs and devices and, subject to reporting and inspection under regulations lawfully issued pursuant to section 505(i) or (k), section 507(d) or (g), section 519, or 520(g), and data relating to other drugs or devices which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505(j) of the title). A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

Sec. 704(e) Every person required under section 519 or 520(g) to maintain records and every person who is in charge or custody of such records shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and to copy and verify, such records.

Section 704 (f)(1) A person accredited under section 523 to review reports made under section 510(k) and make recommendations of initial classifications of devices to the Secretary shall maintain records documenting the training qualifications of the person and the employees of the person, the procedures used by the person for handling confidential information, the compensation arrangements made by the person, and the procedures used by the person to identify and avoid conflicts of interest. Upon the request of an officer or employee designated by the Secretary, the person shall permit the officer or employee, at all reasonable times, to have access to, to copy, and to verify, the records

Section 512 (1)(1) In the case of any new animal drug for which an approval of an application filed pursuant to subsection (b) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to experience, including experience with uses authorized under subsection (a)(4)(A), and other data or information, received or otherwise obtained by such applicant with respect to such drug, or with respect to animal feeds bearing or containing such drug, as the Secretary may by general regulation, or by

order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is any ground for invoking subsection (a) or subsection (m)(4) of this section. Such regulation or order shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this subsection to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to a copy and verify such records.

² Applicable sections of Parts F and G of Title III Public Health Service Act [42 U.S.C. 262-264] are quoted below:

Part F - Licensing - Biological Products and Clinical Laboratories and *****

Sec. 351(c) "Any officer, agent, or employee of the Department Health & Human Services, authorized by the Secretary for the purpose may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any virus, serum toxin, antitoxin, vaccine, blood, blood component or derivatively allergenic product, or other product aforesaid for sale, barter, exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or in any foreign country, or from any foreign country into any State possession."

Part F - *****Control of Radiation.

Sec. 360 A(a) "If the Secretary finds for good cause that the methods, tests, or programs related to electronic product radiation safety in particular factory, warehouse, or establishment in which electronic products are manufactured or held, may not be adequate or reliable officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner operator, or agent in charge, are thereafter authorized (1) to enter, reasonable times any area in such factory, warehouse, or establishment in which the manufacturer's tests (or testing programs) required by section 358(h) are carried out, and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, facilities and procedures within such area which are related to electronic product radiation safety. Each such inspection shall be commenced and completed with reasonable promptness. In addition other grounds upon which good cause may be found for purposes of this subsection, good cause will be considered to exist in any case where the manufacturer has introduced into commerce any electronic product which does not comply with an applicable standard prescribed under this subpart and with respect to which no exemption from notification requirements has been granted by the Secretary under section 359(a)(2) or 359(e)."

(b) "Every manufacturer of electronic products shall establish and maintain such records (including testing records), make such reports, and provide such information, as the Secretary may reasonably require to enable him to determine whether such manufacturer has acted or is acting in compliance with this subpart and standards prescribed pursuant to this subpart and shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee to inspect appropriate books, papers, records, and documents relevant to determining whether such manufacturer has acted or is acting in compliance with standards prescribed pursuant to section 359(a)."

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		1. DISTRICT OFFICE ADDRESS & PHONE NO 900 Madison Ave Baltimore, MD 21201 410-962-3396	
2. NAME AND TITLE OF INDIVIDUAL John P. O'Donnell Ph.D. Exec. VP Research + Quality Control		3. DATE 7-18-01	
4. FIRM NAME Mylan Pharmaceuticals, Inc		5. HOUR 1:30 p.m.	6. NUMBER AND STREET 3711 Collins Ferry Rd
6. NUMBER AND STREET			
7. CITY AND STATE & ZIP CODE Morgantown, WV 26505		8. PHONE # & AREA CODE 304-599-2595	

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)]¹ and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264]²

9. SIGNATURE (Food and Drug Administration Employee(s)) <i>William L Berg</i> <i>Dennis L Dolysnik</i>	10. TYPE OR PRINT NAME AND TITLE (FDA Employee(s)) William L Berg Investigator Dennis L Dolysnik Investigator
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¹ Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:

Sec. 704. (a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, or restricted devices are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use or, restricted devices which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this Act), and research data (other than data relating to new drugs, antibiotic drugs and devices and, subject to reporting and inspection under regulations lawfully issued pursuant to section 505(i) or (k), section 507(d) or (g), section 519, or 520(g), and data relating to other drugs or devices which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505(j) of the title). A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

Sec 704(e) Every person required under section 519 or 520(g) to maintain records and every person who is in charge or custody of such records shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and to copy and verify, such records.

Section 704 (f)(1) A person accredited under section 523 to review reports made under section 510(k) and make recommendations of initial classifications of devices to the Secretary shall maintain records documenting the training qualifications of the person and the employees of the person, the procedures used by the person for handling confidential information, the compensation arrangements made by the person, and the procedures used by the person to identify and avoid conflicts of interest. Upon the request of an officer or employee designated by the Secretary, the person shall permit the officer or employee, at all reasonable times, to have access to, to copy, and to verify, the records.

Section 512 (1)(1) In the case of any new animal drug for which an approval of an application filed pursuant to subsection (b) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to experience, including experience with uses authorized under subsection (e)(4)(A), and other data or information, received or otherwise obtained by such applicant with respect to such drug, or with respect to animal feeds bearing or containing such drug, as the Secretary may by general regulation, or by

order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is cause to be ground for invoking subsection (e) or subsection (m)(4) of this section. Such regulation or order shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this subsection to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

² Applicable sections of Parts F and G of Title III Public Health Service Act [42 U.S.C. 262-264] are quoted below:

Part F - Licensing - Biological Products and Clinical Laboratories and.....

Sec. 351(c) "Any officer, agent, or employee of the Department of Health & Human Services, authorized by the Secretary for the purpose may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession."

Part F -Control of Radiation.

Sec. 360 A(a) "If the Secretary finds for good cause that the methods, tests, or programs related to electronic product radiation safety in a particular factory, warehouse, or establishment in which electronic products are manufactured or held, may not be adequate or reliable, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are thereafter authorized (1) to enter, at reasonable times any area in such factory, warehouse, or establishment in which the manufacturer's tests (or testing programs) required by section 358(h) are carried out, and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, the facilities and procedures within such area which are related to electronic product radiation safety. Each such inspection shall be commenced and completed with reasonable promptness. In addition to other grounds upon which good cause may be found for purposes of this subsection, good cause will be considered to exist in any case where the manufacturer has introduced into commerce any electronic product which does not comply with an applicable standard prescribed under this subpart and with respect to which no exemption from the notification requirements has been granted by the Secretary under section 359(a)(2) or 359(e)."

(b) "Every manufacturer of electronic products shall establish and maintain such records (including testing records), make such reports, and provide such information, as the Secretary may reasonably require to enable him to determine whether such manufacturer has acted or is acting in compliance with this subpart and standards prescribed pursuant to this subpart and shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee to inspect appropriate books, papers, records, and documents relevant to determining whether such manufacturer has acted or is acting in compliance with standards prescribed pursuant to section 359(a)."

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		1. DISTRICT OFFICE ADDRESS & PHONE NO 900 Madison Ave. Baltimore, MD 21201 410-962-3396	
2. NAME AND TITLE OF INDIVIDUAL John P. O'Donnell P.h.D. Exec VP Research & Quality Control		3. DATE 7-19-01	
4. FIRM NAME Mylan Pharmaceuticals Inc		6. HOUR 8:15 a.m.	8. PHONE # & AREA CODE 304-599-259
6. NUMBER AND STREET 3711 Collins Ferry Rd			
7. CITY AND STATE & ZIP CODE Morgantown, WV 26505			

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374(a)]¹ and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264]²

9 SIGNATURE (Food and Drug Administration Employee(s)) <i>William A. Warnick</i>	10 TYPE OR PRINT NAME AND TITLE (FDA Employee(s)) William A. Warnick, Investigator
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Section 704 (f)(1) A person accredited under section 523 to review reports made under section 510(k) and make recommendations of initial classifications of devices to the Secretary shall maintain records documenting the training qualifications of the person and the employees of the person, the procedures used by the person for handling confidential information, the compensation arrangements made by the person, and the procedures used by the person to identify and avoid conflicts of interest. Upon the request of an officer or employee designated by the Secretary, the person shall permit the officer or employee, at all reasonable times, to have access to, to copy, and to verify, the records

Section 512 (1)(1) In the case of any new animal drug for which an approval of an application filed pursuant to subsection (b) is in effect, the applicant shall establish and maintain such records, and shall report to the Secretary, of data relating to experience, including experience with uses authorized under subsection (a)(4)(A), and other data or information, received or otherwise obtained by such applicant with respect to such drug, or with respect to animal feeds bearing or containing such drug, as the Secretary may by general regulation, or by

order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is cause to be ground for invoking subsection (a) or subsection (m)(4) of this section. Such regulation or order shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this subsection to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

² Applicable sections of Parts F and G of Title III Public Health Service Act [42 U.S.C. 262-264] are quoted below:

Part F - Licensing - Biological Products and Clinical Laboratories and

Sec. 351(c) "Any officer, agent, or employee of the Department of Health & Human Services, authorized by the Secretary for the purpose may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession."

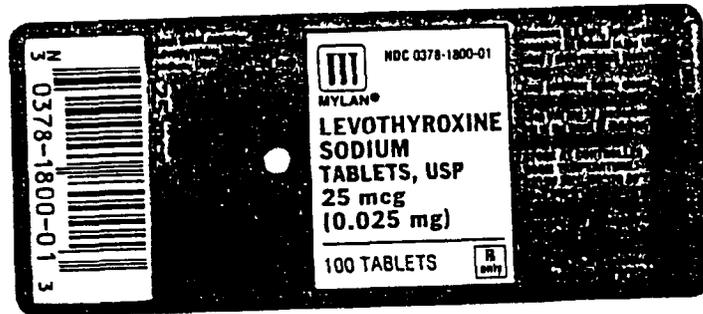
Part F -Control of Radiation.

Sec. 360 A(a) "If the Secretary finds for good cause that the methods, tests, or programs related to electronic product radiation safety in a particular factory, warehouse, or establishment in which electronic products are manufactured or held, may not be adequate or reliable officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are thereafter authorized (1) to enter, at reasonable times any area in such factory, warehouse, or establishment in which the manufacturer's tests (or testing programs) required by section 358(h) are carried out, and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, the facilities and procedures within such area which are related to electronic product radiation safety. Each such inspection shall be commenced and completed with reasonable promptness. In addition to other grounds upon which good cause may be found for purposes of this subsection, good cause will be considered to exist in any case where the manufacturer has introduced into commerce any electronic product which does not comply with an applicable standard prescribed under this subpart and with respect to which no exemption from the notification requirements has been granted by the Secretary under section 359(a)(2) or 359(a)."

(b) "Every manufacturer of electronic products shall establish and maintain such records (including testing records), make such reports, and provide such information, as the Secretary may reasonably require to enable him to determine whether such manufacturer has acted or is acting in compliance with this subpart and standards prescribed pursuant to this subpart and shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee to inspect appropriate books, papers, records, and documents relevant to determining whether such manufacturer has acted or is acting in compliance with standards prescribed pursuant to section 359(a)."



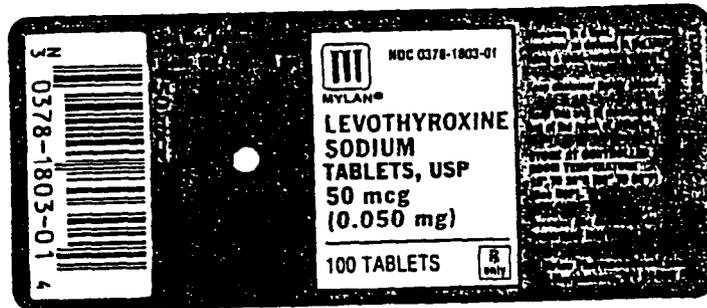
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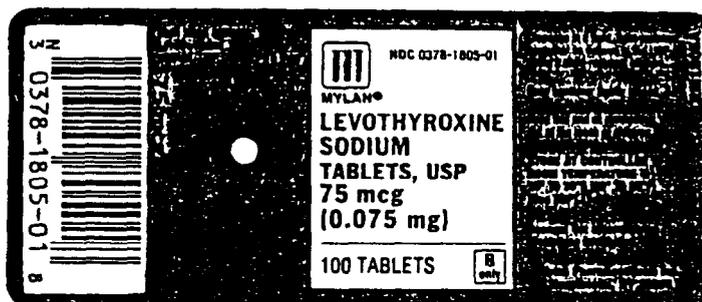
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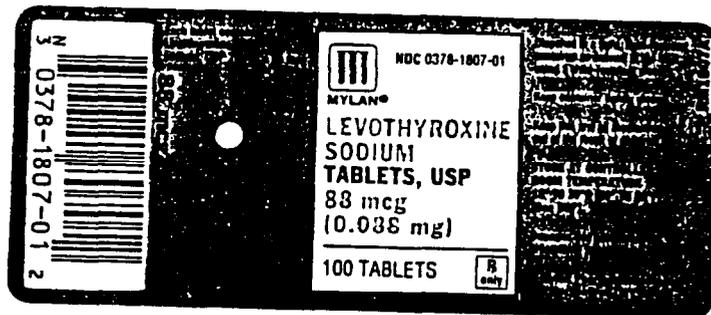
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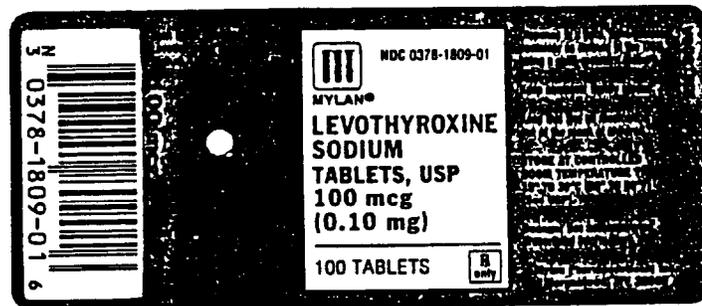
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MYLAN PHARMACEUTICALS INC.



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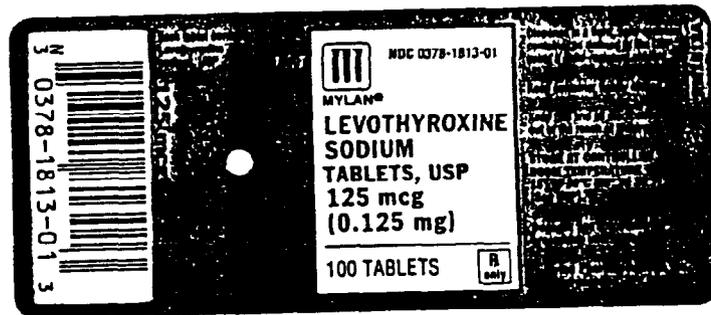
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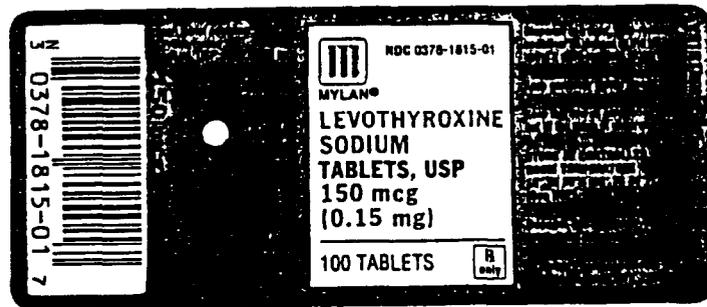
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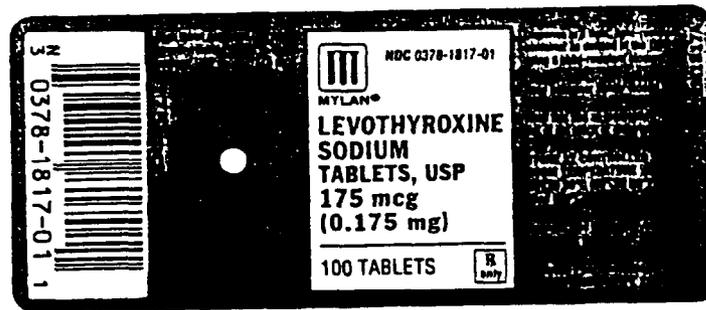
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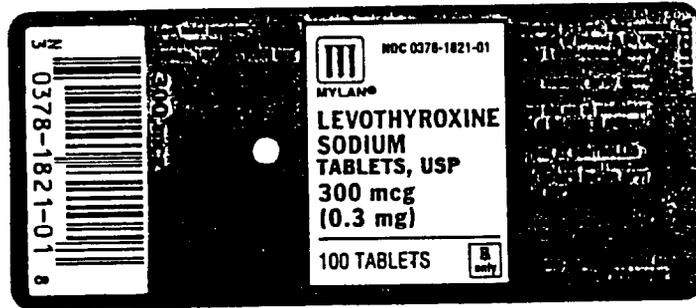
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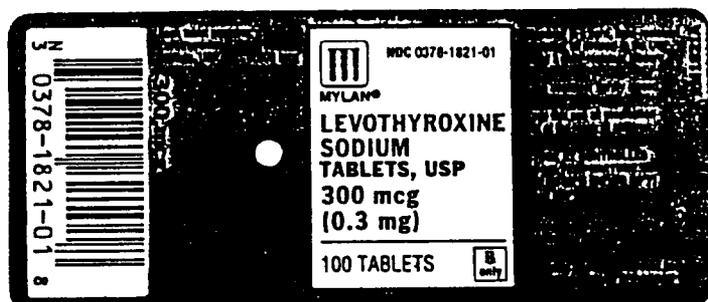
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MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

FEB 28 2002

Robert G. Kowalski, R.Ph.
Acting Executive Director
NJ Drug Utilization Review Council
Market & Warren Streets
CN 360, Room 501
Trenton, NJ 08625-0360

RE: **Levothyroxine Sodium Tablets, USP 25, 50, 75, 88, 100, 112, 125, 150,
175, 200 & 300 mcg**

Dear Mr. Kowalski:

Mylan Pharmaceuticals, Inc. is anticipating FDA approval of the referenced product. Enclosed please find our application and other pertinent information for your review.

If you have any questions or need additional information, please do not hesitate to contact me at (800) 796-9526. My fax number is (304) 285-6437.

Thank you for your assistance.

Sincerely,

Stephen B. Krinke, R.Ph.
Director, Trade Relations
and Government Affairs

0699

Department—Fax Numbers

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Administration (304) 599-7284
Business Development (304) 599-7284
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(304) 285-6409
(304) 598-3232

Biodata Analysis

Drug Name Levothyroxine Sodium Tablets Strength Dosed in Study 600 µg (8 x 75 µg)

Manufacturer Mylan Pharmaceuticals, Inc. Assay Method Used Validated RIA

FASTED DATA		NUMBER OF SUBJECTS IN STUDY = 33			Page # 6
L-triiodothyronine in serum Page #'s 6 and 9	Generic ¹	Reference ¹	GM Ratio (%) ²	90% CI	
Ln AUC 0-l _{dc}	72.89	72.86	100	95.7% - 105%	
	Page # 45	Page # 45	Page # 45	Page # 47	
Ln C _{max}	1.771	1.785	99.2	93.9% - 105%	
	Page # 45	Page # 45	Page # 45	Page # 47	
T _{max} ³	10.43	12.99			
	Page # 45	Page # 45			

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¹ Geometric Mean calculated as exp(LSMEAN), where LSMEAN is the Least Squares Mean from ANOVA analysis of ln-transformed parameters

² GM Ratio is the geometric mean ratio calculated as exp(LSMEAN ln Generic - LSMEAN ln Reference) x 100

³ Mean for TMAX is the Least Squares Mean from ANOVA

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FASTING STUDY

**SINGLE-DOSE BIOEQUIVALENCE INVESTIGATION COMPARING
MYLAN LEVOTHYROXINE SODIUM TABLETS WITH JEROME STEVENS
LEVOTHYROXINE SODIUM TABLETS, USP**

Introduction

Levothyroxine sodium¹ is the sodium salt of the levo isomer of the thyroid hormone thyroxine (T₄). Levothyroxine sodium was first introduced into the market before 1962 without an approved NDA. Orally administered levothyroxine sodium is used as replacement therapy in patients with diminished or absent thyroid function. Levothyroxine sodium may also be used for supplemental therapy for patients with hypothyroidism, which affects approximately 7% of the U.S. population².

The mechanisms by which thyroid hormones exert their physiologic actions have not been completely elucidated³. The physiologic effects of thyroid hormones are produced primarily by T₃, a large portion of which is derived from the deiodination of T₄ in peripheral tissues. The synthesis and secretion of the major thyroid hormones, L-thyroxine (T₄) and L-triiodothyronine (T₃), from the normally functioning thyroid gland are regulated by complex feedback mechanisms of the hypothalamic-pituitary-thyroid axis. The thyroid gland is stimulated to secrete thyroid hormones by the action of thyrotropin (thyroid stimulation hormone, TSH), which is produced in the anterior pituitary gland. TSH secretion is in turn controlled by thyrotropin-releasing hormone (TRH) produced in the hypothalamus, circulating thyroid hormones, and possibly other mechanisms. Thyroid hormones circulating in the blood act as feedback inhibitors of both TSH and TRH secretion. Thus, when serum concentrations of T₃ and T₄ are increased, secretion of TSH and TRH decreases. Conversely, when serum thyroid hormone concentrations are decreased, secretion of TSH and TRH is increased. Administration of exogenous thyroid hormones to euthyroid individuals results in suppression of endogenous thyroid hormone secretion. T₄ and T₃ are transported into cells by passive and active mechanisms.

Levothyroxine tablets taken orally provide T₄ which upon absorption cannot be distinguished from T₄ that is secreted endogenously. Absorption of T₄ from the GI tract varies from 48% to 80% of the dose administered³. The extent of absorption is increased in the fasting state and decreased in malabsorption syndromes, such as sprue. Absorption may also decrease with age. A number of human studies have confirmed the importance of an intact jejunum and ileum for T₄ absorption and have shown some absorption from the duodenum³. The degree of T₄ absorption is dependent on the product formulation as well as the character of the intestinal contents, including plasma protein and soluble dietary factors, which bind thyroid hormone making it unavailable for diffusion. Decreased absorption may result from administration of ferrous sulfate, sodium polystyrene sulfonate, aluminum hydroxide, sucralfate or bile acid sequestrants.

More than 99% of circulating hormones are bound to serum proteins. Only unbound thyroid hormone is metabolically active. T₄ is eliminated slowly from the body, with a half-life of 4 to 7 days. T₃ has a half-life of 1 to 2 days. The liver is the major site of degradation for both hormones. T₄ and T₃ are conjugated with glucuronic and sulfuric acids and excreted in the bile. Approximately 70% of T₄ is converted in the periphery to equal amount of T₃ and reverse triiodothyronine (rT₃). Distribution of thyroid hormones in human body tissues and fluids has not been fully elucidated³. T₄ is more extensively and firmly bound to serum proteins than is T₃.

References

1. Federal Register Notice. Prescription drug products, levothyroxine sodium. August 14, 1997 (volume 62, number 157), pages 43535-8.
2. Coopers DS. Thyroid hormone treatment: new insights into an old therapy. JAMA 261:2694-5, 1989.
3. Physicians' Desk Reference. pp. 1374-1377, 1998.

REPORT TITLE: Single-Dose Fasting In Vivo Bioequivalence Study of
Levothyroxine Sodium Tablets (75 µg; Mylan) and
Levothyroxine Sodium Tablets, USP (75 µg; Jerome Stevens)
in Healthy Male Volunteers

PROTOCOL NUMBER: LEVO-0057

SPONSOR: Mylan Pharmaceuticals Inc.
3711 Collins Ferry Road
Morgantown, WV 26505

DRUG STUDIED: Levothyroxine Sodium Tablets, USP, 75 µg
Mylan Pharmaceuticals Inc.
Lot# R1H0747

Levothyroxine Sodium Tablets, USP, 75 µg
Jerome Stevens Pharmaceuticals (Jerome Stevens)
Lot# 004100

INVESTIGATOR
AND STUDY SITE: James D. Carlson, Pharm.D.
PRACS Institute, Ltd.
2615 N. University Drive
Fargo, North Dakota 58102

ANALYTICAL
SITE: MDS Pharma Services Inc.
2350 Cohen Street
St. Laurent, Quebec
H4R 2N6, Canada

DATE OF STUDY: Clinical Period 1: October 6, 2000 – October 9, 2000
Clinical Period 2: November 17, 2000 – November 20, 2000

Analytical Phase:
L-thyroxine: November 28, 2000 – December 7, 2000
L-triiodothyronine: November 30, 2000 – December 15, 2000

STUDY SUMMARY

The objective of this study was to investigate the bioequivalence of Mylan's levothyroxine sodium 75 µg tablets to Jerome Stevens' levothyroxine sodium 75 µg tablets, USP following a single 600 µg (8 x 75 µg) dose administration in healthy volunteers under fasting conditions. Thirty-three healthy, non-smoking, subjects between the ages of 18 and 45 completed this open-label, randomized, two-period, two-treatment, single-dose crossover study conducted by James D. Carlson, Pharm. D., at PRACS Institute, Ltd., Fargo, ND.

Thirty-six non-smoking, adult, volunteers between the ages of 18 and 50 were accepted into the clinical phase of this study. Male subjects were at least 60 kg (132 lbs) and female subjects were at least 52 kg (115 lbs) and within 15% of their ideal body weight, as referenced by the Table of "Desirable Weights of Adults" by the Metropolitan Life Insurance Company, 1983. All subjects were judged normal (euthyroid) and healthy during a prestudy medical evaluation (physical examination, laboratory evaluation, blood chemistry, serum T₄ (free and total), serum T₃ (total only), serum thyroid-stimulating hormone (TSH), serum thyroxine-binding globulin (TBG), hepatitis B and hepatitis C tests, HIV test, 12-lead ECG, and urine drug screen including amphetamine, barbiturates, benzodiazepine, cannabinoid, cocaine, opiate screen, phencyclidine, and methadone).

Women of childbearing potential had a negative urine pregnancy test on the morning of each dosing day. A third urine pregnancy test was conducted at the end of the study. Women of childbearing potential must also have a negative serum (Beta HCG) prestudy pregnancy test within 14 days prior to the start of the study and used a barrier method of contraception (e.g. condom with spermicide, diaphragm, IUD, etc.) or abstinence. Oral contraceptives were not to be used due to the fact that they increase serum TBG concentrations.

Subjects who were considered ineligible for the study were institutionalized subjects; had abnormal and clinically significant laboratory test results or ECG tracings; had abnormal thyroid function tests; received any surgical treatment within 6 months prior to the initial dose of study medication; had donated more than 450 mL of blood or plasma within 28 days prior to the initial dose of study medication; practiced the use of any tobacco products; had a history of drug and/or alcohol abuse; had any change in dietary or exercise habits throughout the duration of the study; had used any medication within the last 14 days prior to the initial dose of study medication, during the study or during the washout period that may include the following: infant soybean formula, steroids, salicylates, androgenic or estrogenic hormones including oral contraceptives; preparations containing iodine, such as cholestyramine, sucralfate, propranolol, amiodarone, phenytoin, carbamazepine, furosemide, aluminum-containing antacids, including aluminum hydroxide; rifampin, calcium channel blockers and ferrous sulfate; had used any medication known to alter hepatic enzyme activity within 28 days prior to the initial dose of study medication; had a history of any significant chronic disease and/or hepatitis; had a history of any thyroid disease; had a history of any underlying medical condition known to interfere with the absorption or metabolism of thyroid hormones; had an acute illness at the time of either the prestudy medical evaluation or dosing; had consumed vitamins, alcohol,

caffeine- or xanthine-containing foods or beverages within 48 hours prior to the initial dose of study medication; experienced allergy or hypersensitivity to thyroid preparations; had received investigational drug within 30 days prior to the initial dose of study medication. Before study participation, each subject signed a written informed consent. The randomization schedule is listed in Table 5. The subjects were randomly assigned to the following treatments:

Treatment A = Mylan Levothyroxine Sodium Tablets, 75 µg
600 µg (8 x 75 µg), Fasting Administration
Lot #R1H0747, Exp. TBE
Theoretical Lot Size: 500,000
Manufacturing Date: 3/15/00
Assay Potency: 99.5%

Treatment B = Jerome Stevens Levothyroxine Sodium Tablets, USP 75 µg
600 µg (8 x 75 µg), Fasting Administration
Lot #004100, Exp. 04/02
Commercial Lot
Assay Potency: 95.0%

Subjects were housed from the evening prior to dosing until 24 hours after dosing. Subjects were dosed in one enrollment. After a supervised overnight fast (approximately 12.5 hours) each subject received a single, oral 600 µg (8 x 75 µg) dose of either Mylan's levothyroxine sodium tablets (Lot #R1H0747) or Jerome Stevens levothyroxine sodium tablets, USP (Lot #004100) with 240 mL of room temperature water. Subjects received a standard meal 4.25 hours post-dose followed by an evening meal 10 hours after dosing. No fluid except that given with the drug administration was allowed from 1 hour prior to dose administration until 1 hour after dosing. At 2 hours post-dose, all subjects consumed 240 mL of water. There was a forty-two day washout between doses. Period 1 was dosed on October 7, 2000 and Period 2 was dosed on November 18, 2000. Serial blood samples, 14 mL (2 x 7 mL), were collected at the following times relative to dosing: -0.5, -0.25, 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 18, 24, and 48 hours post-dose. Blood samples were collected in vacutainers without anticoagulant, allowed to clot for 30 minutes, centrifuged, and the serum pipetted into duplicate polypropylene tubes, frozen and stored at -80°C or lower until shipment for analysis.

Thirty-six subjects were accepted for entrance into the study. Subject #12 elected to withdraw just prior to Period 1 dosing secondary to fainting during the pre-dose blood draw. Subject #22 was dropped by the medical investigator just prior to Period 1 dosing secondary to impetigo. Thirty-four subjects were dosed in this study. Subject #27 elected to withdraw during Period 1. Therefore, thirty-three subjects completed this study. Twenty-four post-dose adverse events were experienced by thirteen subjects during the study. Fourteen adverse events were listed as mild in severity and nine adverse events were listed as moderate in severity. Six of the adverse events were listed as probably study drug related. One adverse event was listed as possibly drug related. One adverse event was listed as remotely drug related and sixteen adverse events were listed as unrelated to the study drug. There were no serious or life threatening adverse events

reported for this study.

Total L-thyroxine

Samples were assayed at the Immunochemistry Department of MDS Pharma Services, St. Laurent, Quebec, Canada from the period November 28, 2000 to December 7, 2000 for the analysis of total L-thyroxine. The method developed for the analysis of total L-thyroxine in human serum was performed using a validated radioimmunoassay (RIA) method. The standard range of quantitation was from 10.015 ng/mL to 300.462 ng/mL, with an LLOQ of 16.025 ng/mL. The between-batch precision, was 12.1% or less. The between-batch accuracy, reported as %nom, varied within 90.5% and 106.6% of the nominal concentration.

Total L-triiodothyronine

Samples were assayed at the Immunochemistry Department of MDS Pharma Services Inc., St. Laurent, Quebec, Canada, from the period of November 30, 2000 to December 15, 2000 for the analysis of total L-triiodothyronine. The method developed for the analysis of total L-triiodothyronine in human serum was performed using a validated radioimmunoassay (RIA) method. The standard range of quantitation was from 0.250 ng/mL to 8.000 ng/mL, with an LLOQ of 0.500 ng/mL. The between-batch precision was 10.5% or less. The between-batch accuracy, reported as %nom, varied within 92.0% and 106.6% of the nominal concentration.

Single-dose pharmacokinetic parameters for baseline uncorrected total L-thyroxine and baseline uncorrected total L-triiodothyronine were calculated using noncompartmental techniques. The maximum concentration (CPEAK) and the time at which it occurred relative to the administered dose (TPEAK) were determined from the observed plasma concentration-time profile over the sampling time interval. Area under the plasma concentration-time curve (AUC_{0-48}) was the sum of the linear trapezoidal estimation of the areas from the time of dosing to 48 hours post-dose. AUC_{0-48} is equal to AUCL in the statistical output. The predose concentration was obtained by averaging the concentration values at -0.5 hours, -0.25 hours and 0 hours before dosing.

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tested for treatment effects in the parameter means at an alpha level of 0.05. The parameters: AUC_{0-48} , CPEAK and TPEAK, were analyzed statistically using the non-transformed data. The natural log transformed parameters: $LNAUC_{0-48}$ and $LNCPEAK$ were also analyzed. The tests were performed to analyze for statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed using the two one-sided tests procedure.

Data are presented for thirty-three subjects. Because the time deviation exceeded the limit based on R&D-PK-MAP-003, the following actual sampling times were used in the PK analysis at the 0.5 and 1.0 hour protocol times for total L-thyroxine and total L-triiodothyronine: 0.58 hour for Subject #2, Period 2; 1.07 hour for Subject #4, Period 1;

1.07 hour for Subject #10, Period 1; 1.1 hour for Subject #13, Period 1; and 0.57 hour for Subject #18, Period 2. An actual sampling time (51.88 hour) was used in the PK analysis for Subjects #36 at the 48 hour protocol time of Period 1 for total L- triiodothyronine because the time deviation exceeded the limit based on R&D-PK-MAP-003. Subsequently, the serum L-triiodothyronine value at 48 hours for subject #36 was interpolated in order to calculate AUC_{0-48} . The mean concentration versus time profiles (Table 1 for L-thyroxine and Table 2 for L-triiodothyronine) are illustrated graphically in Figure 1 for L-thyroxine and Figure 2 for L-triiodothyronine. Mean plasma profiles are similar between Mylan's 75 μg levothyroxine sodium tablets and Jerome Stevens' levothyroxine sodium 75 μg tablets, USP following a single, oral 600 μg (8 x 75 μg) dose under fasting conditions.

Single-dose pharmacokinetic parameters were analyzed using ANOVA. A summary of the pharmacokinetic parameters are shown in Table 3 for baseline uncorrected total L-thyroxine and Table 4 for baseline uncorrected total L-triiodothyronine. The test and reference formulations demonstrate similar mean pharmacokinetic parameters and variability under fasting conditions. The 90% confidence intervals for L-thyroxine and L-triiodothyronine fall within 80%-125% for the test to reference ratio for the natural log transformed parameters $LNAUC_{0-48}$ and $LNCPEAK$. This study demonstrated that Mylan's 75 μg levothyroxine sodium tablets are bioequivalent to Jerome Stevens' levothyroxine sodium tablets, USP 75 μg following a single, oral 600 μg (8 x 75 μg) dose under fasting conditions.

TABLE 1

LEVOTHYROXINE Na (LEVO-0057)
 Mean L-Thyroxine Serum Concentrations (ng/mL)

Draw Time	Treatment				A VS B P(T >c)
	A (Levothyroxine Na Mylan SR1ND747)		B (Levothyroxine Na. USP Jerome Stevens #004100)		
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	
-0.50 hours	84.54	14.60	83.56	16.90	0.5776
-0.25 hours	82.85	17.95	83.94	14.45	0.5165
0.00 hours	85.09	15.57	82.42	14.06	0.0622
0.50 hours	91.62	17.68	93.99	18.11	0.4373
1.00 hours	115.83	17.21	133.25	20.75	0.0001
1.50 hours	129.89	18.95	147.82	20.09	0.0001
2.00 hours	139.88	16.58	149.48	16.14	0.0016
2.50 hours	142.52	18.13	149.31	12.79	0.0808
3.00 hours	143.64	14.57	148.24	13.25	0.1978
4.00 hours	142.89	16.04	144.25	13.35	0.7247
6.00 hours	135.45	14.47	137.58	12.62	0.3909
8.00 hours	128.28	12.92	128.77	14.02	0.8136
12.00 hours	124.42	14.11	127.76	14.05	0.2055
18.00 hours	115.00	13.31	116.96	15.94	0.3977
24.00 hours	117.86	14.81	119.86	16.36	0.3203
48.00 hours	112.15	13.61	111.56	14.46	0.7245

TABLE 2

LEVOTHYROXINE Na [LEVO-0057]
 Mean L-triiodothyronine Serum Concentrations (ng/mL)

Draw Time	Treatment				A VS B P(T >C)
	A (Levothyroxine Na-- Mylan 9RLH0747)		B (Levothyroxine Na, USP-- Jerome Stevens 9006100)		
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	
-0.50 hours	1.50	19.36	1.52	28.59	0.8266
-0.25 hours	1.51	25.60	1.40	16.65	0.1432
0.00 hours	1.46	16.61	1.48	27.17	0.7632
0.50 hours	1.54	22.47	1.43	18.23	0.1089
1.00 hours	1.51	17.96	1.52	17.47	0.8707
1.50 hours	1.60	22.39	1.51	19.95	0.1296
2.00 hours	1.60	12.94	1.60	26.31	0.9970
2.50 hours	1.59	17.84	1.58	17.82	0.8951
3.00 hours	1.60	17.67	1.53	17.52	0.1713
4.00 hours	1.57	14.48	1.53	19.04	0.5366
6.00 hours	1.60	12.85	1.56	19.57	0.4437
8.00 hours	1.53	17.46	1.51	20.40	0.6868
12.00 hours	1.53	18.15	1.55	18.73	0.7287
18.00 hours	1.51	17.79	1.52	20.53	0.8183
24.00 hours	1.54	17.68	1.57	22.76	0.6098
48.00 hours	1.51	16.47	1.52	16.63	0.7723

TABLE 3

MEAN (%CV) BASELINE UNCORRECTED TOTAL L-THYROXINE PHARMACOKINETIC PARAMETERS IN THIRTY-THREE HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 600 µg (8 x 75 µg) DOSE OF LEVOTHYROXINE SODIUM TABLETS UNDER FASTING CONDITIONS

(PROTOCOL LEVO-0057)

Parameter	Arithmetic Mean A = Mylan	Arithmetic Mean B = Levothyroxine Sodium Tablets, USP***	LSMEANS Ratio (A/B)	90% Confidence Interval**
AUC ₀₋₄₈ (ng x hr/mL)	5734 (12.77)	5824 (13.88)	0.99	96% - 101%
CPEAK (ng/mL)	155.4 (15.56)	160.8 (15.21)	0.97	94% - 100%
TPEAK (hr)	3.394 (48.27)	2.485 (52.40)	-----	-----

* Ratio (A/B) = $e^{(LSMEAN \text{ of LNA} - LSMEAN \text{ of LNB})}$

**Used Natural Log Transformed Parameter

***Manufactured by Jerome Stevens

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TABLE 4

MEAN (%CV) BASELINE UNCORRECTED TOTAL L-TRIIODOTHYRONINE PHARMACOKINETIC PARAMETERS IN THIRTY-THREE HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 600 µg (8 x 75 µg) DOSE OF LEVOTHYROXINE SODIUM TABLETS UNDER FASTING CONDITIONS
(PROTOCOL LEVO-0057)

Parameter	Arithmetic Mean A = Mylan	Arithmetic Mean B = Levothyroxine Sodium Tablets, USP***	LSMEANS Ratio (A/B)	90% Confidence Interval**
AUC ₀₋₄₈ (ng x hr/mL)	73.52 (14.24)	73.95 (17.42)	1.00	96% - 105%
CPEAK (ng/mL)	1.800 (20.09)	1.817 (21.06)	0.99	94% - 105%
TPEAK (hr)	10.48 (134.0)	12.88 (119.7)	-----	-----

* Ratio (A/B) = e^[LSMEAN of LNA - LSMEAN of LNB]

**Used Natural Log Transformed Parameter

***Manufactured by Jerome Stevens

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TABLE 5
Levothyroxine Sodium Tablets, 75 ug [LEVO-0057]

Randomization Schedule

Dosing Phase 1 2

Group 1
Subjects

1	B	A
2	B	A
3	A	B
4	A	B
5	A	B
6	A	B
7	B	A
8	B	A
9	B	A
10	A	B
11	B	A
12	A	B
13	A	B
14	B	A
15	A	B
16	B	A
17	B	A
18	A	B
19	B	A
20	A	B
21	B	A
22	A	B
23	A	B
24	B	A
25	B	A
26	A	B
27	B	A
28	A	B
29	A	B
30	A	B
31	B	A
32	B	A
33	B	A

Prepared By: *[Signature]*

Date: 9/22/2000

Treatments

A: Levothyroxine Sodium 75 ug Tablets, 8 x 75 ug, Mylan

B: Levothyroxine Sodium 75 ug Tablets, USP, 8 x 75 ug, Jerome Stevens

TABLE 5 (continued)
Levothyroxine Sodium Tablets, 75 ug [LEVO-0057]

Randomization Schedule

Dosing Phase	1	2
Group 1 Subjects		
34	B	A
35	A	B
36	A	B
37	A	B
38	A	B
39	B	A
40	B	A

Prepared By:  Lin Date: 9/22/2000

Treatments

- A: Levothyroxine Sodium 75 ug Tablets, 8 x 75 ug, Mylan
- B: Levothyroxine Sodium 75 ug Tablets, USP, 8 x 75 ug, Jerome Stevens

FIGURE 1: MEAN L-THYROXINE PLASMA CONCENTRATION

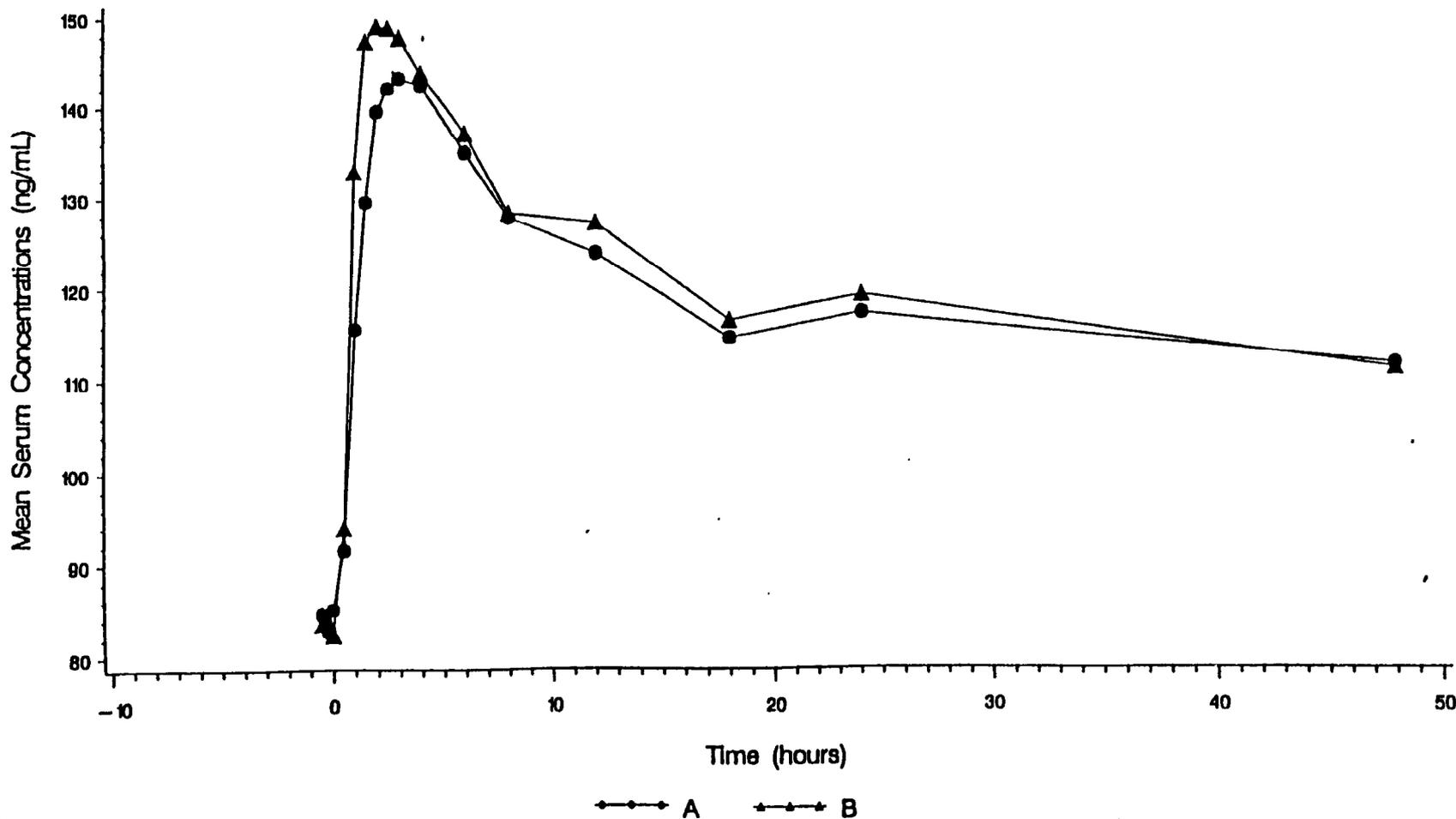
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LEVOTHYROXINE Na (LEVO-0057)

Total Dose: 600 ug (8x75ug Tablets), Study Type: Fasting

Mean L-thyroxine Serum Concentrations

N=33



Treatment A is A (Levothyroxine Na--Mylan #R1H0747)

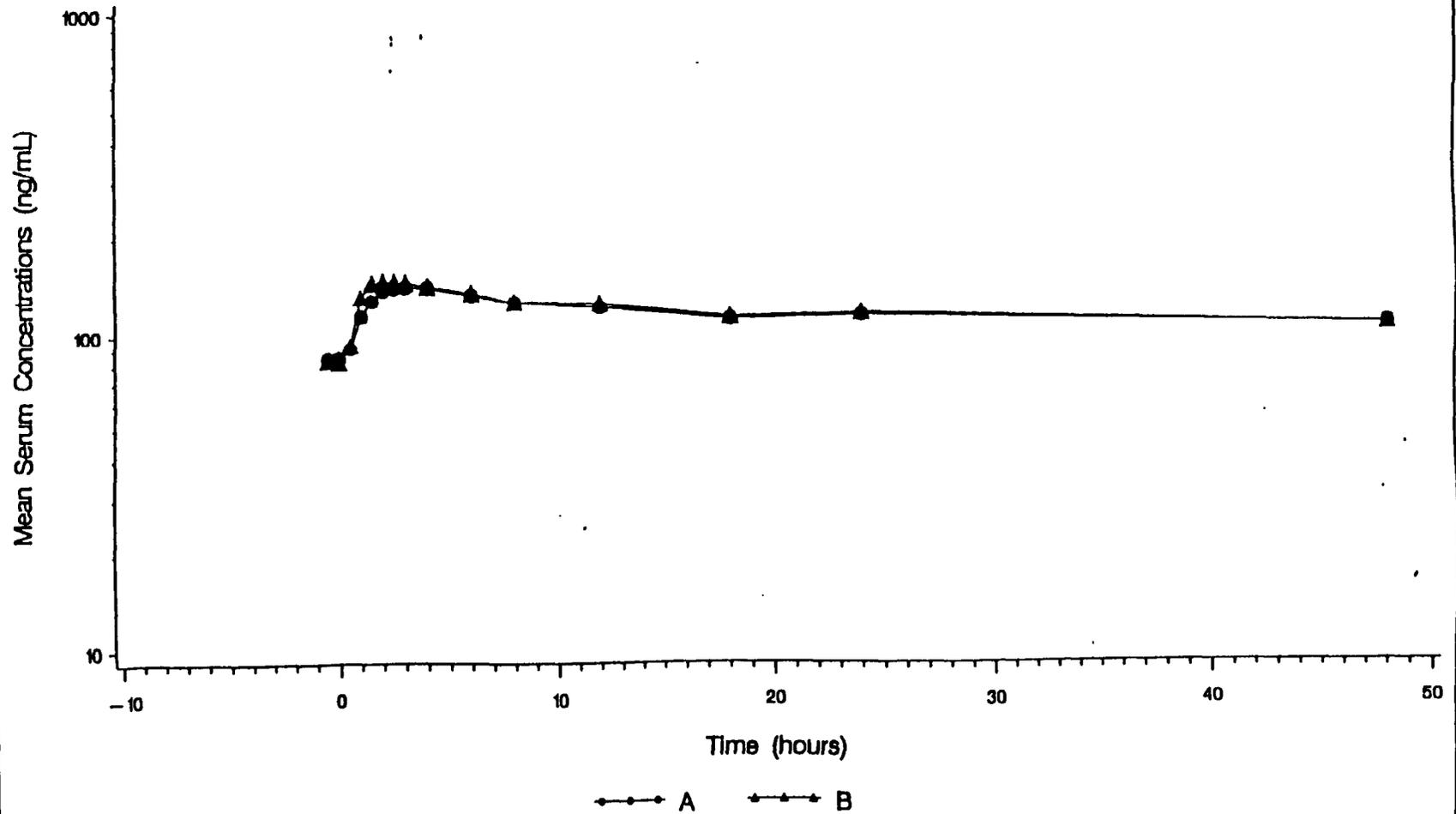
Treatment B is B (Levothyroxine Na, USP--Jerome Stevens #004100)

LEVOTHYROXINE Na (LEVO-0057)

Total Dose: 600 ug (8x75ug Tablets), Study Type: Fasting

Mean L-thyroxine Serum Concentrations

N=33



Treatment A is A (Levothyroxine Na—Mylan #R1H0747)

Treatment B is B (Levothyroxine Na, USP—Jerome Stevens #004100)

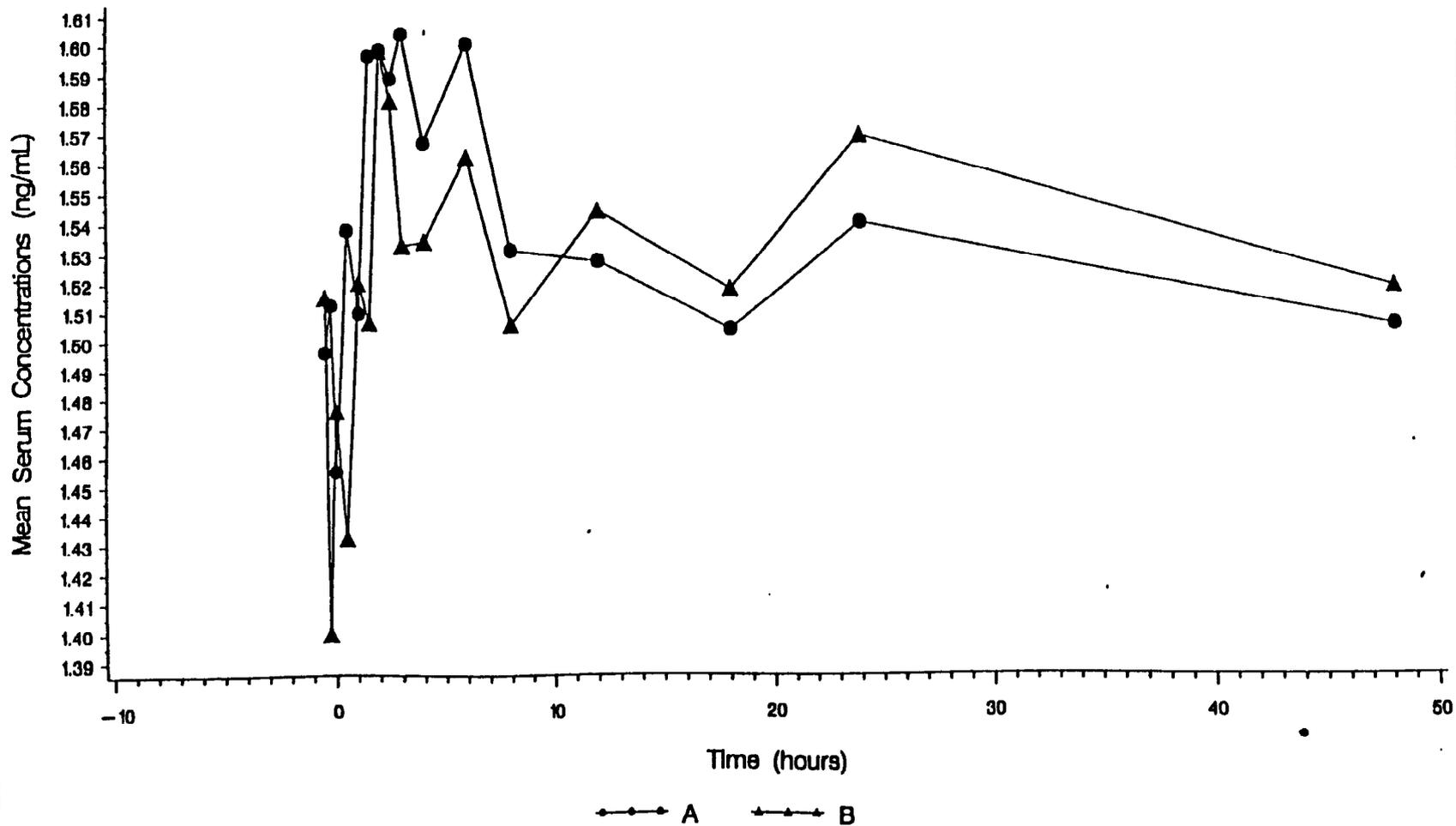
FIGURE 2: MEAN L-TRIIODOTHYRONINE PLASMA CONCENTRATION

LEVOTHYROXINE Na (LEVO-0057)

Total Dose: 600 ug (8x75ug Tablets), Study Type: Fasting

Mean L-triiodothyronine Serum Concentrations

N=33



Treatment A is A (Levothyroxine Na--Mylan #R1H0747)

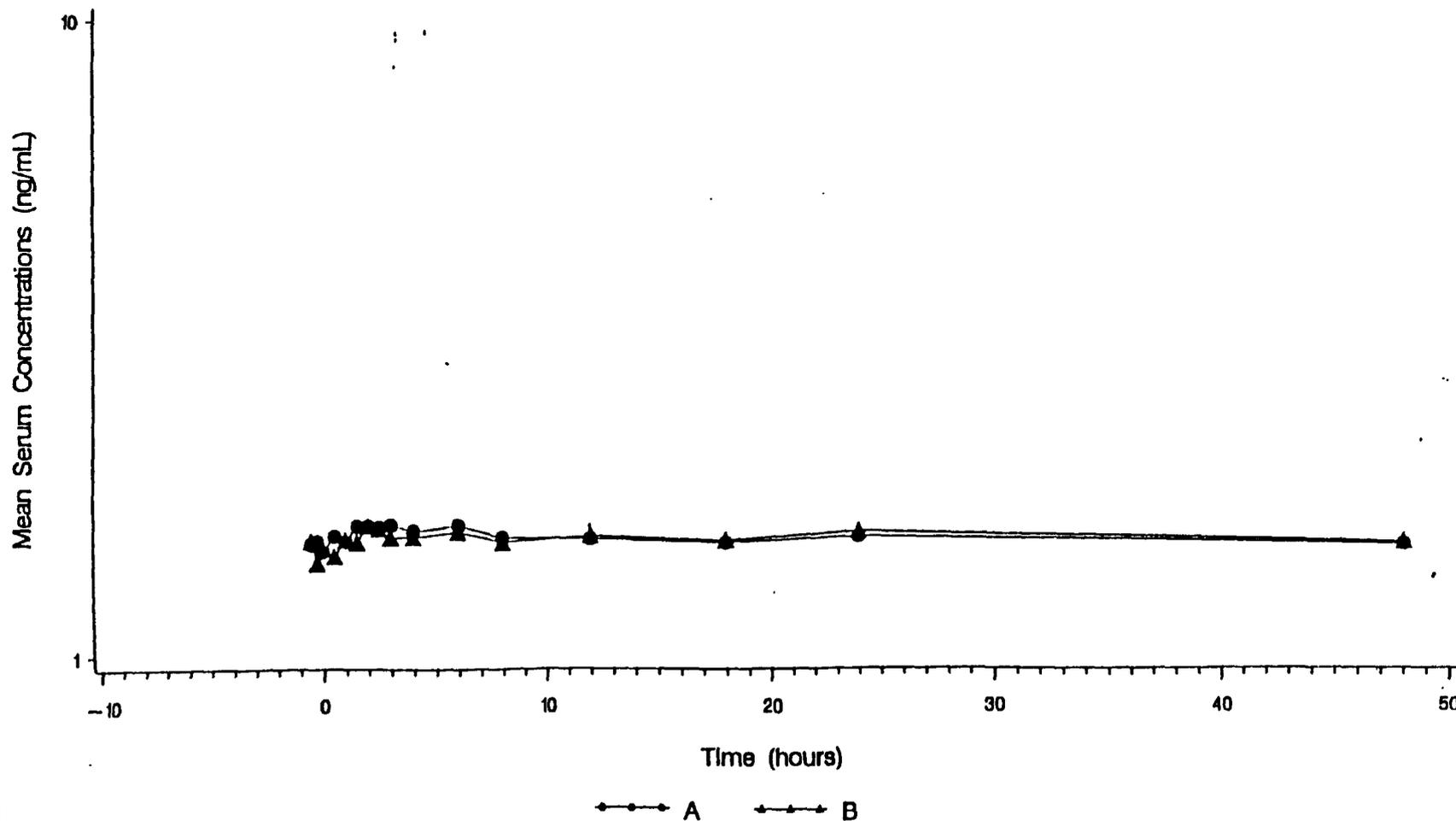
Treatment B is B (Levothyroxine Na, USP--Jerome Stevens #004100)

LEVOTHYROXINE Na (LEVO-0057)

Total Dose: 600 ug (8x75ug Tablets), Study Type: Fasting

Mean L-triiodothyronine Serum Concentrations

N=33



Treatment A is A (Levothyroxine Na--Mylan #R1H0747)

Treatment B is B (Levothyroxine Na, USP--Jerome Stevens #004100)

STATISTICAL ANALYSIS: L-THYROXINE

- A. Mean Data and Indices of Variance
- B. Analysis of Variance
- C. Confidence Intervals

STATISTICAL ANALYSIS: L-THYROXINE

A. Mean Data and Indices of Variance

LEVOTHYROXINE Na [LEVO-0057]
 L-thyroxine Serum
 Subject Concentration Profiles
 Mean Data Arranged by the Treatment Variable
 03/08/01

----- TREAT=A -----

Variable	Label	N	Mean	Std Dev	CV
CONC1	-0.50 hours	33	84.5373636	12.3432825	14.6009787
CONC2	-0.25 hours	33	82.8473939	14.8726854	17.9519050
CONC3	0.00 hours	33	85.0936364	13.2460626	15.5664549
CONC4	0.50 hours	33	91.6155758	16.1949657	17.6770877
CONC5	1.00 hours	33	115.8346970	19.9296041	17.2052111
CONC6	1.50 hours	33	129.8937576	24.6180508	18.9524511
CONC7	2.00 hours	33	139.8755455	23.1882761	16.5777914
CONC8	2.50 hours	33	142.5219091	25.8354951	18.1273850
CONC9	3.00 hours	33	143.6419091	20.9355633	14.5748295
CONC10	4.00 hours	33	142.8868788	22.9219659	16.0420369
CONC11	6.00 hours	33	135.4500000	19.5960578	14.4673738
CONC12	8.00 hours	33	128.2838485	16.5722758	12.9184430
CONC13	12.00 hours	33	124.4228485	17.5615764	14.1144305
CONC14	18.00 hours	33	114.9982424	15.3017387	13.3060631
CONC15	24.00 hours	33	117.8557576	17.1047635	14.5133033
CONC16	48.00 hours	33	112.1471515	15.2578057	13.6051656

----- TREAT=B -----

Variable	Label	N	Mean	Std Dev	CV
CONC1	-0.50 hours	33	83.5627879	14.1194030	16.8967592
CONC2	-0.25 hours	32	83.9429375	12.1258398	14.4453365
CONC3	0.00 hours	33	82.4153333	11.5835870	14.0551358
CONC4	0.50 hours	33	93.9887879	17.0212338	18.1098556
CONC5	1.00 hours	33	133.2527879	27.6512945	20.7510063
CONC6	1.50 hours	33	147.8166667	29.7025344	20.0941714
CONC7	2.00 hours	33	149.4767576	24.1309879	16.1436388
CONC8	2.50 hours	33	149.3135758	19.0996891	12.7916628
CONC9	3.00 hours	33	148.2403939	19.6357684	13.2458960
CONC10	4.00 hours	33	144.2465455	19.2639827	13.3549006
CONC11	6.00 hours	33	137.5831212	17.3698398	12.6249787
CONC12	8.00 hours	33	128.7747273	18.0490217	14.0159658
CONC13	12.00 hours	33	127.7629697	17.9567193	14.0547134
CONC14	18.00 hours	33	116.9563939	18.6404136	15.9379175
CONC15	24.00 hours	33	119.8612424	19.6139644	16.3638921
CONC16	48.00 hours	33	111.5611212	16.1328937	14.4610358

LEVOthyroxINE Na [LEVO-0057]
L-thyroxine Serum
Noncompartmental Pharmacokinetics Parameters
Mean Data Arranged by the Treatment Variable
03/08/01

----- TREAT=A -----

Variable	N	Mean	Std Dev	CV
AUCL	33	5734.25	732.0018160	12.7654315
AUCI	0	.	.	.
CPEAK	33	155.4162727	24.1777827	15.5567897
TPEAK	33	3.3939394	1.6382039	48.2685087
KEL	0	.	.	.
HALF	0	.	.	.
LNAUCL	33	8.6464058	0.1265973	1.4641610
LNAUCI	0	.	.	.
LNCPEAK	33	5.0351750	0.1477450	2.9342570

----- TREAT=B -----

Variable	N	Mean	Std Dev	CV
AUCL	33	5823.94	808.5387613	13.8830195
AUCI	0	.	.	.
CPEAK	33	160.7952727	24.4581778	15.2107567
TPEAK	33	2.4848485	1.3019508	52.3955790
KEL	0	.	.	.
HALF	0	.	.	.
LNAUCL	33	8.6604642	0.1384764	1.5989488
LNAUCI	0	.	.	.
LNCPEAK	33	5.0696347	0.1452962	2.8660083

STATISTICAL ANALYSIS: L-THYROXINE

B. Analysis of Variance

LEVOTHYROXINE Na [LEVO-0057]
L-thyroxine Serum Variables
03/08/01

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SEQ	2	1 2
TREAT	2	A B
PER	2	1 2
SUB	33	01 02 03 04 05 06 07 08 09 10 11 13 14 15 16 17 18 19 20 21 23 24 25 26 28 29 30 31 32 33 34 35 36

Number of observations in data set = 66

Group	Obs	Dependent Variables
0	0	AUCI KEL HALF LNAUCI
1	66	AUCL CPEAK TPEAK LNAUCL LNCPEAK

NOTE: Variables in each group are consistent with respect to the presence or absence of missing values.

LEVOTHYROXINE Na [LEVO-0057]
 L-thyroxine Serum Variables
 03/08/01

General Linear Models Procedure

Dependent Variable: AUCL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	34	35714285.5	1050420.2	13.11	0.0001
Error	31	2484415.6	80142.4		
Corrected Total	65	38198701.0			
	R-Square	C.V.	Root MSE	AUCL Mean	
	0.934961	4.898594	283.094	5779.10	

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	25203.4	25203.4	0.31	0.5790
SUB (SEQ)	31	35555286.3	1146944.7	14.31	0.0001
TREAT	1	132730.3	132730.3	1.66	0.2076
PER	1	1065.5	1065.5	0.01	0.9089

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	25203.4	25203.4	0.31	0.5790
SUB (SEQ)	31	35555286.3	1146944.7	14.31	0.0001
TREAT	1	133329.8	133329.8	1.66	0.2066
PER	1	1065.5	1065.5	0.01	0.9089

Tests of Hypotheses using the Type III MS for SUB (SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	25203.3956	25203.3956	0.02	0.8831

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	-89.9334118	-1.29	0.2066	69.7250435

LEVOTHYROXINE Na [LEVO-0057]
L-thyroxine Serum Variables
03/08/01

General Linear Models Procedure

Dependent Variable: CPEAK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	34	34102.8796	1003.0259	7.36	0.0001
Error	31	4223.0899	136.2287		
Corrected Total	65	38325.9694			
	R-Square	C.V.	Root MSE	CPEAK Mean	
	0.889811	7.382213	11.6717	158.106	

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	123.6345	123.6345	0.91	0.3481
SUB (SEQ)	31	32712.9541	1055.2566	7.75	0.0001
TREAT	1	477.4051	477.4051	3.50	0.0707
PER	1	788.8860	788.8860	5.79	0.0223

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	123.6345	123.6345	0.91	0.3481
SUB (SEQ)	31	32712.9541	1055.2566	7.75	0.0001
TREAT	1	440.5147	440.5147	3.23	0.0819
PER	1	788.8860	788.8860	5.79	0.0223

Tests of Hypotheses using the Type III MS for SUB (SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	123.634479	123.634479	0.12	0.7344

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	-5.16937132	-1.80	0.0819	2.87469541

LEVOTHYROXINE Na [LEVO-0057]
 L-thyroxine Serum Variables
 03/08/01

General Linear Models Procedure

Dependent Variable: TPEAK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	34	113.592594	3.340959	2.58	0.0046
Error	31	40.164982	1.295645		
Corrected Total	65	153.757576			

R-Square	C.V.	Root MSE	TPEAK Mean
0.738777	38.72444	1.13826	2.93939

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	6.7653883	6.7653883	5.22	0.0293
SUB (SEQ)	31	92.2421875	2.9755544	2.30	0.0118
TREAT	1	13.6363636	13.6363636	10.52	0.0028
PER	1	0.9486547	0.9486547	0.73	0.3987

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	6.7653883	6.7653883	5.22	0.0293
SUB (SEQ)	31	92.2421875	2.9755544	2.30	0.0118
TREAT	1	13.8425941	13.8425941	10.68	0.0026
PER	1	0.9486547	0.9486547	0.73	0.3987

Tests of Hypotheses using the Type III MS for SUB (SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	6.76538826	6.76538826	2.27	0.1417

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	0.91636029	3.27	0.0026	0.28034993

LEVOTHYROXINE Na (LEVO-0057)
 L-thyroxine Serum Variables
 03/08/01

General Linear Models Procedure

Dependent Variable: LNAUCL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	34	1.04639171	0.03077623	11.45	0.0001
Error	31	0.08335206	0.00268878		
Corrected Total	65	1.12974377			

R-Square	C.V.	Root MSE	LNAUCL Mean
0.926220	0.599223	0.05185	8.65344

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00066510	0.00066510	0.25	0.6224
SUB (SEQ)	31	1.04242358	0.03362657	12.51	0.0001
TREAT	1	0.00326105	0.00326105	1.21	0.2792
PER	1	0.00004198	0.00004198	0.02	0.9014

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00066510	0.00066510	0.25	0.6224
SUB (SEQ)	31	1.04242358	0.03362657	12.51	0.0001
TREAT	1	0.00328050	0.00328050	1.22	0.2778
PER	1	0.00004198	0.00004198	0.02	0.9014

Tests of Hypotheses using the Type III MS for SUB (SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00066510	0.00066510	0.02	0.8891

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	-0.01410677	-1.10	0.2778	0.01277129

LEVOTHYROXINE Na [LEVO-0057]
 L-thyroxine Serum Variables
 03/08/01

General Linear Models Procedure

Dependent Variable: LNCPEAK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	34	1.23890744	0.03643845	7.30	0.0001
Error	31	0.15475141	0.00499198		
Corrected Total	65	1.39365886			

R-Square	C.V.	Root MSE	LNCPEAK Mean
0.888960	1.398422	0.07065	5.05240

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00203335	0.00203335	0.41	0.5280
SUB (SEQ)	31	1.18181651	0.03812311	7.64	0.0001
TREAT	1	0.01959327	0.01959327	3.92	0.0565
PER	1	0.03546432	0.03546432	7.10	0.0121

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00203335	0.00203335	0.41	0.5280
SUB (SEQ)	31	1.18181651	0.03812311	7.64	0.0001
TREAT	1	0.01801098	0.01801098	3.61	0.0668
PER	1	0.03546432	0.03546432	7.10	0.0121

Tests of Hypotheses using the Type III MS for SUB (SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00203335	0.00203335	0.05	0.8189

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	-0.03305417	-1.90	0.0668	0.01740179

LEVOTHYROXINE Na. [LEVO-0057]
L-thyroxine Serum Variables
03/08/01

General Linear Models Procedure
Least Squares Means

TREAT	ADCL LSMEAN	CPEAK LSMEAN	TPEAK LSMEAN	LNAUCL LSMEAN	LNCPEAK LSMEAN
A	5734.72108	155.562581	3.38786765	8.64647786	5.03604605
B	5824.65449	160.731952	2.47150735	8.66058464	5.06910022

STATISTICAL ANALYSIS: L-THYROXINE

C. Confidence Intervals

LEVOthyroxine Na (LEVO-0057)
 Total Dose: 600 ug (8x75ug Tablets), Study Type: Fasting
 L-thyroxine Serum Parameters
 Confidence Intervals / Calculated using Least Square Means
 Data File = ../data/sucdata.dat
 03/08/01

VS	NAME	TESTMEAN	REFMEAN	ESTIMATE	STDEEST	DF	TVALUE	LO	HI
A VS B	AQCL	5734.72	5824.65	-89.9334	69.7250	31	1.69552	96.43	100.49
	CPEAK	155.56	160.73	-5.1694	2.8747	31	1.69552	93.75	99.82
	LQADCL	8.65	8.66	-0.0141	0.0128	31	1.69552	96.49	100.76
	LQCPEAK	5.04	5.07	-0.0331	0.0174	31	1.69552	93.94	99.65

Treatment A is A (Levothyroxine Na--Mylan #RLH0747)
 Treatment B is B (Levothyroxine Na, USP--Jerome Stevens #004100)

STATISTICAL ANALYSIS: L-TRIIODOTHYRONINE

- A. Mean Data and Indices of Variance
- B. Analysis of Variance
- C. Confidence Intervals

STATISTICAL ANALYSIS: L-TRIIODOTHYRONINE

A. Mean Data and Indices of Variance

LEVOTYROXINE Na [LEVO-0057]
 L-triiodothyronine Serum
 Subject Concentration Profiles
 Mean Data Arranged by the Treatment Variable
 04/03/01

----- TREAT=A -----

Variable	Label	N	Mean	Std Dev	CV
CONC1	-0.50 hours	33	1.4965455	0.2897687	19.3625036
CONC2	-0.25 hours	33	1.5127879	0.3872215	25.5965492
CONC3	0.00 hours	33	1.4550909	0.2417317	16.6128239
CONC4	0.50 hours	33	1.5384848	0.3457169	22.4712599
CONC5	1.00 hours	33	1.5101515	0.2711714	17.9565711
CONC6	1.50 hours	33	1.5972424	0.3576488	22.3916439
CONC7	2.00 hours	33	1.5992121	0.2068878	12.9368557
CONC8	2.50 hours	33	1.5898182	0.2836604	17.8423163
CONC9	3.00 hours	33	1.6048788	0.2836241	17.6726159
CONC10	4.00 hours	33	1.5680303	0.2270715	14.4813211
CONC11	6.00 hours	33	1.6015758	0.2057942	12.8494826
CONC12	8.00 hours	33	1.5320000	0.2675153	17.4618344
CONC13	12.00 hours	33	1.5285152	0.2774035	18.1485599
CONC14	18.00 hours	33	1.5050909	0.2677828	17.7918048
CONC15	24.00 hours	33	1.5413939	0.2725633	17.6829091
CONC16	48.00 hours	33	1.5067879	0.2481856	16.4711728

----- TREAT=B -----

Variable	Label	N	Mean	Std Dev	CV
CONC1	-0.50 hours	33	1.5155152	0.4332252	28.5860023
CONC2	-0.25 hours	32	1.3995313	0.2329531	16.6450823
CONC3	0.00 hours	33	1.4761818	0.4011492	27.1747803
CONC4	0.50 hours	33	1.4321515	0.2610162	18.2254583
CONC5	1.00 hours	33	1.5205758	0.2655917	17.4665206
CONC6	1.50 hours	33	1.5071212	0.3007199	19.9532686
CONC7	2.00 hours	33	1.5989697	0.4206940	26.3103192
CONC8	2.50 hours	33	1.5822121	0.2821326	17.8315274
CONC9	3.00 hours	33	1.5335455	0.2686941	17.5211027
CONC10	4.00 hours	33	1.5348788	0.2922972	19.0436688
CONC11	6.00 hours	32	1.5632188	0.3058737	19.5669131
CONC12	8.00 hours	33	1.5063636	0.3073348	20.4024306
CONC13	12.00 hours	33	1.5453333	0.2894705	18.7319129
CONC14	18.00 hours	33	1.5190606	0.3118828	20.5312930
CONC15	24.00 hours	33	1.5709091	0.3575365	22.7598454
CONC16	48.00 hours	33	1.5199394	0.2527904	16.6316118

LEVOTHYROXINE Na [LEVO-0057]
 L-triiodothyronine Serum
 Noncompartmental Pharmacokinetics Parameters
 Mean Data Arranged by the Treatment Variable
 04/03/01

----- TREAT=A -----

Variable	N	Mean	Std Dev	CV
AUCL	33	73.5211515	10.4695901	14.2402423
AUCI	0	.	.	.
CPEAK	33	1.7999394	0.3615877	20.0888834
TPEAK	33	10.4848485	14.0504030	134.0067343
KEL	0	.	.	.
HALF	0	.	.	.
LNAUCL	33	4.2876186	0.1439392	3.3570902
LNAUCI	0	.	.	.
LNCPEAK	33	0.5712808	0.1776021	31.0884122

----- TREAT=B -----

Variable	N	Mean	Std Dev	CV
AUCL	33	73.9456061	12.8848295	17.4247399
AUCI	0	.	.	.
CPEAK	33	1.8170606	0.3827280	21.0630261
TPEAK	33	12.8787879	15.4161190	119.7016295
KEL	0	.	.	.
HALF	0	.	.	.
LNAUCL	33	4.2884242	0.1762646	4.1102424
LNAUCI	0	.	.	.
LNCPEAK	33	0.5791850	0.1863334	32.1716498

STATISTICAL ANALYSIS: L-TRIIODOTHYRONINE

B. Analysis of Variance

LEVOTHYROXINE Na [LEVO-0057]
 L-triiodothyronine Serum Variables
 04/03/01

General Linear Models Procedure
 Class Level Information

Class	Levels	Values
SEQ	2	1 2
TREAT	2	A B
PER	2	1 2
SUB	33	01 02 03 04 05 06 07 08 09 10 11 13 14 15 16 17 18 19 20 21 23 24 25 26 28 29 30 31 32 33 34 35 36

Number of observations in data set = 66

Group	Obs	Dependent Variables
0	0	AUCI KEL HALF LNAUCI
1	66	AUCL CPEAK TPEAK LNAUCL LNCPEAK

NOTE: Variables in each group are consistent with respect to the presence or absence of missing values.

LEVOTHYROXINE Na [LEVO-0057]
L-triiodothyronine Serum Variables
04/03/01

General Linear Models Procedure

Dependent Variable: AUCL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	34	6952.64745	204.48963	3.39	0.0005
Error	31	1870.52198	60.33942		
Corrected Total	65	8823.16942			
	R-Square	C.V.	Root MSE		AUCL Mean
	0.787999	10.53505	7.76785		73.7334

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	243.96345	243.96345	4.04	0.0531
SUB (SEQ)	31	6614.12359	213.35883	3.54	0.0004
TREAT	1	2.97267	2.97267	0.05	0.8258
PER	1	91.58773	91.58773	1.52	0.2272

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	243.96345	243.96345	4.04	0.0531
SUB (SEQ)	31	6614.12359	213.35883	3.54	0.0004
TREAT	1	2.05448	2.05448	0.03	0.8548
PER	1	91.58773	91.58773	1.52	0.2272

Tests of Hypotheses using the Type III MS for SUB(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	243.963450	243.963450	1.14	0.2932

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	-0.35302757	-0.18	0.8548	1.91318991

LEVOTHYROXINE Na [LEVO-0057]
 L-triiodothyronine Serum Variables
 04/03/01

General Linear Models Procedure

Dependent Variable: CPEAK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	34	6.21497452	0.18279337	2.13	0.0181
Error	31	2.66110598	0.08584213		
Corrected Total	65	8.87608050			
	R-Square	C.V.	Root MSE	CPEAK Mean	
	0.700194	16.20062	0.29299	1.80850	

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.01736291	0.01736291	0.20	0.6560
SUB (SEQ)	31	6.17717809	0.19926381	2.32	0.0109
TREAT	1	0.00483674	0.00483674	0.06	0.8139
PER	1	0.01559677	0.01559677	0.18	0.6729

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.01736291	0.01736291	0.20	0.6560
SUB (SEQ)	31	6.17717809	0.19926381	2.32	0.0109
TREAT	1	0.00537277	0.00537277	0.06	0.8041
PER	1	0.01559677	0.01559677	0.18	0.6729

Tests of Hypotheses using the Type III MS for SUB (SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.01736291	0.01736291	0.09	0.7698

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	-0.01805331	-0.25	0.8041	0.07216187

LEVOTHYROXINE Na [LEVO-0057]
 L-triiodothyronine Serum Variables
 04/03/01

General Linear Models Procedure

Dependent Variable: TPEAK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	34	9721.43583	285.92458	2.06	0.0223
Error	31	4295.38235	138.56072		
Corrected Total	65	14016.81818			

R-Square	C.V.	Root MSE	TPEAK Mean
0.693555	100.7650	11.7712	11.6818

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	58.98178	58.98178	0.43	0.5189
SUB (SEQ)	31	9035.33640	291.46246	2.10	0.0211
TREAT	1	94.56061	94.56061	0.68	0.4151
PER	1	532.55704	532.55704	3.84	0.0590

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	58.98178	58.98178	0.43	0.5189
SUB (SEQ)	31	9035.33640	291.46246	2.10	0.0211
TREAT	1	108.55704	108.55704	0.78	0.3829
PER	1	532.55704	532.55704	3.84	0.0590

Tests of Hypotheses using the Type III MS for SUB(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	58.9817848	58.9817848	0.20	0.6559

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	-2.56617647	-0.89	0.3829	2.89919607

LEVOTHYROXINE Na [LEVO-0057]
L-triiodothyronine Serum Variables
04/03/01

General Linear Models Procedure

Dependent Variable: LNAUCL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	34	1.30277923	0.03831704	3.35	0.0005
Error	31	0.35443850	0.01143350		
Corrected Total	65	1.65721773			

R-Square	C.V.	Root MSE	LNAUCL Mean
0.786124	2.493634	0.10693	4.28802

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.03567624	0.03567624	3.12	0.0872
SUB (SEQ)	31	1.24295668	0.04009538	3.51	0.0004
TREAT	1	0.00001071	0.00001071	0.00	0.9758
PER	1	0.02413561	0.02413561	2.11	0.1563

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.03567624	0.03567624	3.12	0.0872
SUB (SEQ)	31	1.24295668	0.04009538	3.51	0.0004
TREAT	1	0.00000206	0.00000206	0.00	0.9894
PER	1	0.02413561	0.02413561	2.11	0.1563

Tests of Hypotheses using the Type III MS for SUB (SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.03567624	0.03567624	0.89	0.3528

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	0.00035392	0.01	0.9894	0.02633584

LEVOTHYROXINE Na [LEVO-0057]
 L-triiodothyronine Serum Variables
 04/03/01

General Linear Models Procedure

Dependent Variable: LNCPEAK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	34	1.57206937	0.04623733	2.61	0.0042
Error	31	0.54936602	0.01772148		
Corrected Total	65	2.12143539			
	R-Square	C.V.	Root MSE	LNCPEAK Mean	
	0.741040	23.14229	0.13312	0.57523	

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00273682	0.00273682	0.15	0.6970
SUB (SEQ)	31	1.56784529	0.05057565	2.85	0.0023
TREAT	1	0.00103087	0.00103087	0.06	0.8110
PER	1	0.00045640	0.00045640	0.03	0.8735

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00273682	0.00273682	0.15	0.6970
SUB (SEQ)	31	1.56784529	0.05057565	2.85	0.0023
TREAT	1	0.00098879	0.00098879	0.06	0.8148
PER	1	0.00045640	0.00045640	0.03	0.8735

Tests of Hypotheses using the Type III MS for SUB(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00273682	0.00273682	0.05	0.8176

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	-0.00774481	-0.24	0.8148	0.03278744

LEVOTHYROXINE Na [LEVO-0057]
L-triiodothyronine Serum Variables
04/03/01

General Linear Models Procedure
Least Squares Means

TREAT	AUCL LSMEAN	CPEAK LSMEAN	TPEAK LSMEAN	LNAUCL LSMEAN	LNCPEAK LSMEAN
A	73.6151526	1.79996507	10.4273897	4.28890324	0.57155572
B	73.9681801	1.81801838	12.9935662	4.28854932	0.57930053

STATISTICAL ANALYSIS: L-TRIIODOTHYRONINE

C. Confidence Intervals

LEVOTHYROXINE Na (LEVO-0057)
 Total Dose: 600 ug (8x75ug Tablets), Study Type: Fasting
 L-triiodothyronine Serum Parameters
 Confidence Intervals / Calculated using Least Square Means
 Data File = ../data/aucdata.dat
 04/03/01

VS	NAME	TESTMEAN	REFMEAN	ESTIMATE	STDEEST	DF	TVALUE	LO	HI
A VS B	AUCL	73.6152	73.9682	-0.35303	1.91319	31	1.69552	95.14	103.91
	CPEAK	1.8000	1.8180	-0.01805	0.07216	31	1.69552	92.28	105.74
	LNAUCL	4.2889	4.2885	0.00035	0.02634	31	1.69552	95.67	104.60
	LNCPEAK	0.5716	0.5793	-0.00774	0.03279	31	1.69552	93.86	104.90

Treatment A is A (Levothyroxine Na--Mylan #RLH0747)
 Treatment B is B (Levothyroxine Na, USP--Jerome Stevens #004100)

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 5, 2001

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: LEVOTHYROXINE SODIUM TABLETS, USP
25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG,
125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

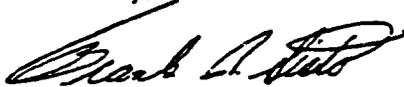
Dear Mr. Buehler:

Pursuant to 21 CFR Paragraph 320.22(d)(2) of the bioavailability and bioequivalency requirements, we request a waiver of the *in vivo* bioequivalence testing requirements for Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 88mcg, 100mcg, 112mcg, 150mcg, 175mcg and 200mcg.

Mylan has established the *in vivo* bioequivalence of the levothyroxine drug product by comparing our 75mcg, 125mcg and 300mcg strengths to the Jerome Stevens manufactured tablets, 75mcg (Thyrox® Tablets), 125mcg (Levotab® Tablets) and 300mcg (Thyrox® Tablets) in fasting *in vivo* bioequivalence studies. Based on discussions with senior management within OGD, the formulations for the Jerome Stevens Thyrox® and Levotab® products are the same as approved in the Jerome Stevens NDA for Unithroid® Tablets. Mylan's Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 88mcg, 100mcg, 112mcg, 150mcg, 175mcg and 200mcg are proportionally similar to our 75mcg, 125mcg and 300mcg products, as defined in the Agency's Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, dated October, 2000.

A comparative formulation table is attached. Also attached are dissolution profiles and f_2 analysis, and a dissolution profile summary comparing the formulations for Mylan's Levothyroxine Sodium Tablets, USP with that of Unithroid® Tablets. The referenced formulations meet the *in vitro* dissolution requirements established by this application.

Sincerely,



Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

0749

G:\PROJECT\ANDA\LEVOTHYROXINE\SECTIONS-01THRU07.doc

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MYLAN Pharmaceuticals Inc.
781 Chestnut Ridge Road
POB 4310
Morgantown, WV 26504-4310

Single-Dose In Vivo Bioequivalence Study of
Levothyroxine Sodium Tablets (125 ug; MYLAN)
and Levothyroxine Sodium Tablets, USP (125 ug;
Jerome Stevens) in Health Volunteers

Fasting Study

Protocol # LEVO-0054

0750

Biodata Analysis

Drug Name Levothyroxine Sodium Tablets Strength Dosed in Study 500 µg (4 x 125 µg)

Manufacturer Mylan Pharmaceuticals, Inc. Assay Method Used Validated RIA

FASTED DATA		NUMBER OF SUBJECTS IN STUDY = 30			Page #6
L-thyroxine in serum	Generic ¹	Reference ¹	GM Ratio (%) ²	90% CI	
Page #'s 6 and 8					
Ln AUC 0-l _{dc}	5435	5481	99.2	97.1%-101%	
	Page #30	Page #30	Page #30	Page #32	
Ln C _{max}	139.3	145.5	95.8	92.8%-98.9%	
	Page #30	Page #30	Page #30	Page #32	
T _{max} ³	3.018	2.705			
	Page #30	Page #30			

¹ Geometric Mean calculated as exp(LSMEAN), where LSMEAN is the Least Squares Mean from ANOVA analysis of ln-transformed parameters

² GM Ratio is the geometric mean ratio calculated as exp(LSMEAN ln Generic - LSMEAN ln Reference) x 100

³ Mean for T_{MAX} is the Least Squares Mean from ANOVA

0751

Biodata Analysis

Drug Name Levothyroxine Sodium Tablets Strength Dosed in Study 500 µg (4 x 125 µg)

Manufacturer Mylan Pharmaceuticals, Inc. Assay Method Used Validated RIA

FASTED DATA		NUMBER OF SUBJECTS IN STUDY = 30			Page #6
L-triiodothyronine in serum Page #'s 6 and 9	Generic ¹	Reference ¹	GM Ratio (%) ²	90% CI	
Ln AUC 0-l _{dc}	65.10	64.89	100	97.8%-103%	
	Page #44	Page #44	Page #44	Page #46	
Ln C _{max}	1.539	1.531	100	96.8%-104%	
	Page #44	Page #44	Page #44	Page #46	
T _{max} ³	8.850	6.904			
	Page #44	Page #44			

¹ Geometric Mean calculated as exp(LSMEAN), where LSMEAN is the Least Squares Mean from ANOVA analysis of ln-transformed parameters

² GM Ratio is the geometric mean ratio calculated as exp(LSMEAN ln Generic – LSMEAN ln Reference) x 100

³ Mean for T_{MAX} is the Least Squares Mean from ANOVA

0752

FASTING STUDY

**SINGLE-DOSE BIOEQUIVALENCE INVESTIGATION COMPARING MYLAN
LEVOTHYROXINE SODIUM TABLETS WITH JEROME STEVENS LEVOTHYROXINE
SODIUM TABLETS, USP**

Introduction

Levothyroxine sodium¹ is the sodium salt of the levo isomer of the thyroid hormone thyroxine (T₄). Levothyroxine sodium was first introduced into the market before 1962 without an approved NDA. Orally administered levothyroxine sodium is used as replacement therapy in patients with diminished or absent thyroid function. Levothyroxine sodium may also be used for supplemental therapy for patients with hypothyroidism, which affects approximately 7% of the U.S. population².

The mechanisms by which thyroid hormones exert their physiologic actions have not been completely elucidated³. The physiologic effects of thyroid hormones are produced primarily by T₃, a large portion of which is derived from the deiodination of T₄ in peripheral tissues. The synthesis and secretion of the major thyroid hormones, L-thyroxine (T₄) and L-triiodothyronine (T₃), from the normally functioning thyroid gland are regulated by complex feedback mechanisms of the hypothalamic-pituitary-thyroid axis. The thyroid gland is stimulated to secrete thyroid hormones by the action of thyrotropin (thyroid stimulation hormone, TSH), which is produced in the anterior pituitary gland. TSH secretion is in turn controlled by thyrotropin-releasing hormone (TRH) produced in the hypothalamus, circulating thyroid hormones, and possibly other mechanisms. Thyroid hormones circulating in the blood act as feedback inhibitors of both TSH and TRH secretion. Thus, when serum concentrations of T₃ and T₄ are increased, secretion of TSH and TRH decreases. Conversely, when serum thyroid hormone concentrations are decreased, secretion of TSH and TRH is increased. Administration of exogenous thyroid hormones to euthyroid individuals results in suppression of endogenous thyroid hormone secretion. T₄ and T₃ are transported into cells by passive and active mechanisms.

Levothyroxine tablets taken orally provide T₄ which upon absorption cannot be distinguished from T₄ that is secreted endogenously. Absorption of T₄ from the GI tract varies from 48% to 80% of the dose administered³. The extent of absorption is increased in the fasting state and decreased in malabsorption syndromes, such as sprue. Absorption may also decrease with age. A number of human studies have confirmed the importance of an intact jejunum and ileum for T₄ absorption and have shown some absorption from the duodenum³. The degree of T₄ absorption is dependent on the product formulation as well as the character of the intestinal contents, including plasma protein and soluble dietary factors, which bind thyroid hormone making it unavailable for diffusion. Decreased absorption may result from administration of ferrous sulfate, sodium polystyrene sulfonate, aluminum hydroxide, sucralfate or bile acid sequestrants.

More than 99% of circulating hormones are bound to serum proteins. Only unbound thyroid hormone is metabolically active. T₄ is eliminated slowly from the body, with a half-life of 4 to 7 days. T₃ has a half-life of 1 to 2 days. The liver is the major site of degradation for both hormones. T₄ and T₃ are conjugated with glucuronic and sulfuric acids and excreted in the bile. Approximately 70% of T₄ is converted in the periphery to equal amount of T₃ and reverse triiodothyronine (rT₃). Distribution of thyroid hormones in human body tissues and fluids has not been fully elucidated³. T₄ is more extensively and firmly bound to serum proteins than is T₃.

References

1. Federal Register Notice. Prescription drug products, levothyroxine sodium. August 14, 1997 (volume 62, number 157), pages 43535-8.
2. Coopers DS. Thyroid hormone treatment: new insights into an old therapy. JAMA 261:2694-5, 1989.
3. Physicians' Desk Reference. pp. 1374-1377, 1998.

REPORT TITLE: Single-Dose Fasting In Vivo Bioequivalence Study of
Levothyroxine Sodium Tablets (125 µg; Mylan) and
Levothyroxine Sodium Tablets, USP (125 µg; Jerome Stevens)
in Healthy Male Volunteers

PROTOCOL NUMBER: LEVO-0054

SPONSOR: Mylan Pharmaceuticals Inc.
3711 Collins Ferry Road
Morgantown, WV 26505

DRUG STUDIED: Levothyroxine Sodium Tablets, 125 µg
Mylan Pharmaceuticals, Inc.
Lot# R1H0750

Levothyroxine Sodium Tablets, USP, 125 µg
Jerome Stevens Pharmaceuticals
Lot# 003799

INVESTIGATOR
AND STUDY SITE: James D. Carlson, Pharm.D.
PRACS Institute, Ltd.
Fargo, North Dakota 58102

ANALYTICAL
SITE: MDS Pharma Services Inc.
2350 Cohen Street
St. Laurent, Quebec
H4R 2N6, Canada

DATE OF STUDY: Clinical Period 1: September 23, 2000 – September 26, 2000
Clinical Period 2: November 4, 2000 – November 7, 2000

Analytical Phase

L-Thyroxine: November 16, 2000 - November 24, 2000
L-Triiodothyronine: November 20, 2000 - November 28, 2000

STUDY SUMMARY

The objective of this study was to investigate the bioequivalence of Mylan's levothyroxine sodium 125 µg tablets to Jerome Stevens' levothyroxine sodium 125 µg tablets, USP following a single 500 µg (4 x 125 µg) dose administration in healthy volunteers. Twenty-seven healthy, non-smoking, subjects between the ages of 18 and 48 completed this open-label, randomized, two-period, two-treatment, single-dose crossover study conducted by James D. Carlson, Pharm. D., at PRACS Institute, Ltd., Fargo, ND.

Thirty non-smoking, adult volunteers between the ages of 18 and 50 were accepted into the clinical phase of this study. Male subjects were at least 60 kg (132 lbs) and female subjects were at least 52 kg (115 lbs) and within 15% of their ideal body weight, as referenced by the Table of "Desirable Weights of Adults" by the Metropolitan Life Insurance Company, 1983. All subjects were judged normal (euthyroid) and healthy during a prestudy medical evaluation (physical examination, laboratory evaluation, blood chemistry, serum T₄ (free and total), serum T₃ (total only), serum thyroid-stimulating hormone (TSH), serum thyroxine-binding globulin (TBG), hepatitis B and hepatitis C tests, HIV test, 12-lead ECG, and urine drug screen including amphetamine, barbiturates, benzodiazepine, cannabinoid, cocaine, opiate screen, phencyclidine, and methadone).

Women of childbearing potential had a negative urine pregnancy test on the morning of each dosing day. A third urine pregnancy test was conducted at the end of each study. Also, women of child-bearing potential had a negative serum (Beta HCG) prestudy pregnancy test within 14 days prior to the start of the study. During the study, women were advised to use barrier methods of contraception (e.g., condoms with spermicide, diaphragm, IUD, etc.) or abstinence. Oral contraceptives were not used due to the fact that they increase serum TBG concentrations, and therefore, elevate T₄.

Subjects who were considered ineligible for the study were institutional subjects; had abnormal and clinically significant laboratory test results or ECG tracings; had abnormal thyroid function tests; received any surgical treatment within 6 months prior to the initial dose of study medication; had donated more than 450 mL of blood or plasma within 28 days prior to the initial dose of study medication; practiced the use of any tobacco products; had a history of drug and/or alcohol abuse; had any change in dietary or exercise habits throughout the duration of the study; had used any medication within the last 14 days prior to the initial dose of study medication, during the study or during the washout period that may include the following: infant soybean formula, steroids, salicylates, androgenic or estrogenic hormones including oral contraceptives; preparations containing iodine, such as vitamins, oral anti-diabetic agents, all resins for lowering of cholesterol, such as cholestyramine; sucralfate, propranolol, amiodarone, phenytoin, carbamazepine, furosemide, aluminum-containing antacids, including aluminum hydroxide; rifampin, calcium channel blockers and ferrous sulfate; had used any medication known to alter hepatic enzyme activity within 28 days prior to the initial dose of study medication; had a history of any significant chronic disease and/or hepatitis; had a history of any thyroid disease; had a history of any underlying medical condition known to interfere with the absorption or metabolism of thyroid hormones; had an acute illness at the time of either the prestudy medical evaluation or dosing; had consumed vitamins, alcohol,

caffeine- or xanthine-containing foods or beverages within 48 hours prior to the initial dose of study medication; experienced allergy or hypersensitivity to thyroid preparations; had received investigational drug within 30 days prior to the initial dose of study medication. Before study participation, each subject signed a written informed consent. The randomization table is listed in Table 5. The subjects were randomly assigned to the following treatments:

Treatment A = Mylan Levothyroxine Sodium Tablets, 125 µg
500 µg (4 x 125 µg), Fasting Administration
Lot #R1H0750, Exp. TBE
Theoretical Lot Size: 500,000 tablets
Manufacturing Date: 3/16/00
Assay Potency: 97.2%

Treatment B = Jerome Stevens Levothyroxine Sodium Tablets, USP 125 µg
500 µg (4 x 125 µg), Fasting Administration
Lot #003799, Exp. 05/02
Commercial Lot
Assay Potency: 94.6%

Subjects were housed from the evening prior to dosing until 24 hours after dosing. Subjects were dosed in one enrollment. After a supervised overnight fast (approximately 12.5 hours) each subject received a single, oral 500 µg (4 x 125 µg) dose of either Mylan's levothyroxine sodium tablets (Lot #R1H0750) or Jerome Stevens levothyroxine sodium tablets, USP (Lot #003799) with 240 mL of room temperature water. Subjects received a standard meal 4.25 hours post-dose followed by an evening meal 10 hours after dosing. No fluid except that given with the drug administration was allowed from 1 hour prior to dose administration until 1 hour after dosing. At 2 hours post-dose, all subjects consumed 240 mL of water. There was a forty-two day washout between doses. Period 1 was dosed on September 24, 2000 and Period 2 was dosed on November 5, 2000. Serial blood samples, 14 mL (2 x 7 mL), were collected at the following times relative to dosing: -0.5, -0.25, 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 18, 24, and 48 hours post-dose. Blood samples were collected in vacutainers without anticoagulant, allowed to clot for 30 minutes, centrifuged, and the serum pipetted into duplicate polypropylene tubes, frozen and stored at approximately -80°C until shipment for analysis.

Thirty subjects were dosed and twenty-seven subjects completed this study. Subjects #'s 2 and 6 failed to report for Period 2 check-in. Subject 03 was dropped by the Sponsor prior to Period 2 dose administration secondary to LASIK eye surgery scheduled for November 27, 2000. Nineteen post-dose adverse events were experienced by thirteen subjects during the study. Fourteen adverse events were listed as unrelated to the study drug. Two adverse events were listed as remotely related. One adverse event was listed as possibly drug related and two adverse events were listed as probably related to the study drug. Thirteen adverse events were listed as mild in severity and six adverse events were listed as moderate in severity. There were no serious or life threatening adverse events reported for this study.

Total L-thyroxine

Samples were assayed at the Immunochemistry Department of MDS Pharma Services Inc., St. Laurent, Quebec, Canada, from the period of November 16, 2000 to November 24, 2000 for the analysis of L-thyroxine. The method developed for the analysis of total L-thyroxine in human serum was performed using a validated radioimmunoassay (RIA) method. The standard range of quantitation was from 10.015 ng/mL to 300.462 ng/mL, with a LLOQ of 16.025 ng/mL. The between-batch precision was 11.4% or less. The between-batch accuracy, reported as %nom, varied within 89.0% and 110.1% of the nominal concentration.

Total L-triiodothyronine

Samples were assayed at the Immunochemistry Department of MDS Pharma Services Inc., 2350 Cohen Street, St. Laurent, Quebec, HAR 2N6, Canada, from the period of November 20, 2000 to November 28, 2000 for the analysis of total L-triiodothyronine. The method developed for the analysis of total L-triiodothyronine in human serum was performed using a validated radioimmunoassay (RIA) method. The standard range of quantitation was from 0.250 ng/mL to 8.000 ng/mL, with a LLOQ of 0.500 ng/mL. For Set 1 (OMU), the between-batch precision was 7.4% or less; and the between-batch accuracy, reported as %nom, varied within 90.2% and 105.1% of the nominal concentration. For Set 2 (OMC), the between-batch precision was not determined; and the between-batch accuracy, reported as %nom, varied within 86.6% and 117.9% of the nominal concentration.

Single-dose pharmacokinetic parameters for baseline uncorrected total L-thyroxine and baseline uncorrected total L-triiodothyronine were calculated using noncompartmental techniques. The maximum concentration (CPEAK) and the time at which it occurred relative to the administered dose (TPEAK) were determined from the observed plasma concentration-time profile over the sampling time interval. Area under the plasma concentration-time curve (AUC_{0-48hr}) was the sum of the linear trapezoidal estimation of the areas from the time of dosing to 48 hours post-dose. AUC_{0-48hr} is equal to the AUCL in the statistical output. The predose concentration was obtained by averaging the concentration values at -0.5 hours, -0.25 hours and 0 hours before dosing.

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tested for treatment effects in the parameter means at an alpha level of 0.05. The parameters: AUC_{0-48hr} , CPEAK, and TPEAK were analyzed statistically using the non-transformed data. The natural log transformed parameters: $LNAUC_{0-48hr}$ and $LNCPEAK$ were also analyzed. The tests were performed to analyze for statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed using the two one-sided tests procedure.

Although twenty-seven subjects completed this study, data are presented for thirty subjects due to the fact that samples from three subjects who dropped after Period 1 were inadvertently analyzed by the analytical laboratory. An actual sampling time (1.07 hour)

was used in the PK analysis for Subject #10 at the 1 hour protocol time because the time deviation exceeded the limit based on R&D-PK-MAP-003. The mean concentration versus time profiles (Table 1 for L-thyroxine and Table 2 for L-triiodothyronine) are illustrated graphically in Figures 1 and 2, respectively. Mean plasma profiles are similar between Mylan's 125 µg levothyroxine sodium tablets and Jerome Stevens' levothyroxine sodium tablets, USP following a single, oral 500 µg (4 x 125 µg) dose under fasting conditions.

Single-dose pharmacokinetic parameters were analyzed using ANOVA. A summary of the pharmacokinetic parameters is shown in Table 3 for baseline uncorrected total L-thyroxine and in Table 4 for baseline uncorrected total L-triiodothyronine. The test and reference formulations demonstrate similar mean pharmacokinetic parameters and variability under fasting conditions.

The 90% confidence intervals for baseline uncorrected total L-thyroxine and baseline uncorrected total L-triiodothyronine fall within 80%-125% for the test to reference ratio for the natural log transformed parameters, $LNAUC_{0-48hr}$ and $LNCPEAK$. This study demonstrated that Mylan's 125 µg levothyroxine sodium tablets are bioequivalent to Jerome Stevens' levothyroxine sodium tablets, USP following a single, oral 500 µg (4 x 125 µg) dose under fasting conditions.

TABLE 1

LEVOTHYROXINE Na [LEVO-0054]
 Mean L-thyroxine Serum Concentrations (ng/mL)

Draw Time	Treatment				A VS B P(Z >C)
	A (Levothyroxine Na-- Mylan 91180750)		B (Levothyroxine Na-- Jecrose Stevens 8003799)		
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	
-0.50 hours	84.43	15.35	82.18	13.64	0.3726
-0.25 hours	83.77	13.17	82.71	13.23	0.8036
0.00 hours	83.57	13.90	82.52	13.52	0.7733
0.50 hours	92.79	17.02	92.00	16.66	0.9615
1.00 hours	113.44	17.43	114.30	16.89	0.0015
1.50 hours	126.67	17.95	138.86	16.29	0.0007
2.00 hours	132.57	16.85	141.95	13.40	0.0085
2.50 hours	133.22	13.32	139.88	10.26	0.0144
3.00 hours	132.98	12.91	137.78	12.29	0.0243
4.00 hours	133.12	13.57	135.47	12.08	0.1610
6.00 hours	130.20	13.89	129.89	11.39	0.7767
8.00 hours	123.43	12.75	122.40	12.18	0.9999
12.00 hours	122.07	14.62	119.63	11.82	0.5194
18.00 hours	110.42	16.97	112.63	10.51	0.2434
24.00 hours	113.57	12.49	114.47	13.33	0.2981
48.00 hours	109.38	12.81	106.13	12.42	0.1192

TABLE 2

LEVOTHYROXINE Na (LEVO-0054)
 Mean L-Triiodothyronine Serum Concentrations (ng/mL)

Draw Time	Treatment				A VS B P(T >c)
	A (Levothyroxine Na-- Mylan 88180750)		B (Levothyroxine Na-- Jerome Stevens 8003799)		
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	
-0.50 hours	1.34	14.64	1.36	17.17	0.4333
-0.25 hours	1.33	12.25	1.35	16.09	0.4240
0.00 hours	1.31	14.56	1.33	17.81	0.5567
0.50 hours	1.39	15.92	1.31	16.44	0.0594
1.00 hours	1.38	15.43	1.38	15.95	0.8080
1.50 hours	1.40	14.86	1.42	17.22	0.5429
2.00 hours	1.46	16.98	1.47	17.79	0.6756
2.50 hours	1.42	14.51	1.44	16.75	0.6890
3.00 hours	1.42	16.64	1.39	16.77	0.3787
4.00 hours	1.42	16.46	1.42	17.14	0.8271
6.00 hours	1.44	13.30	1.43	17.92	0.8539
8.00 hours	1.40	14.26	1.40	17.68	0.7038
12.00 hours	1.39	15.75	1.38	16.92	0.9323
18.00 hours	1.30	15.93	1.33	16.92	0.1538
24.00 hours	1.38	15.19	1.40	18.94	0.5120
48.00 hours	1.39	16.54	1.36	16.32	0.2745

TABLE 3

MEAN (%CV) BASELINE UNCORRECTED TOTAL L-THYROXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 500 µg (4 x 125 µg) DOSE OF LEVOTHYROXINE SODIUM TABLETS UNDER FASTING CONDITIONS (PROTOCOL LEVO-0054)				
Parameter	Arithmetic Mean A = Mylan N=28	Arithmetic Mean B = Jerome Stevens N=29	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUC _{0-48hr} (ng x hr/mL)	5539 (12.47)	5537 (11.66)	0.99	97% - 101%
CPEAK (ng/mL)	142.5 (13.18)	147.1 (12.98)	0.96	93% - 99%
TPEAK (hr)	3.089 (42.03)	2.724 (57.33)	-----	-----

*Ratio (A/B) = e^[LSMEAN of LNA - LSMEAN of LNB]

**Used Natural Log Transformed Parameter

0762

TABLE 4

MEAN (%CV) BASELINE UNCORRECTED TOTAL L-TRIIODOTHYRONINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 500 µg (4 x 125 µg) DOSE OF LEVOTHYROXINE SODIUM TABLETS UNDER FASTING CONDITIONS

(PROTOCOL LEVO-0054)

Parameter	Arithmetic Mean A = Mylan N=28	Arithmetic Mean B = Jerome Stevens N=29	LSMEANS Ratio (A/B)*	90% Confidence Interval**
AUC _{0-48hr} (ng x hr/mL)	66.32 (14.50)	66.18 (17.19)	1.00	98% - 103%
CPEAK (ng/mL)	1.571 (14.03)	1.559 (15.29)	1.00	97% - 104%
TPEAK (hr)	8.964 (157.1)	6.897 (145.0)	----	----

*Ratio (A/B) = e^[LSMEAN of LNA - LSMEAN of LNB]

**Used Natural Log Transformed Parameter

0763

TABLE 5 - continued
Levothyroxine Sodium Tablets, 300 ug [LEVO-0054]

Randomization Schedule

Dosing Phase	1	2
Group 1 Subjects		
34	B	A
35	A	B
36	A	B

Prepared By:  Lin

Date: 8/31/2000

Treatments

- A: Levothyroxine Sodium 300 ug Tablets, 600 ug (2 x 300 ug), Mylan
B: Levothyroxine Sodium 300 ug Tablets, USP, 600 ug (2 x 300 ug), Jerome Stevens

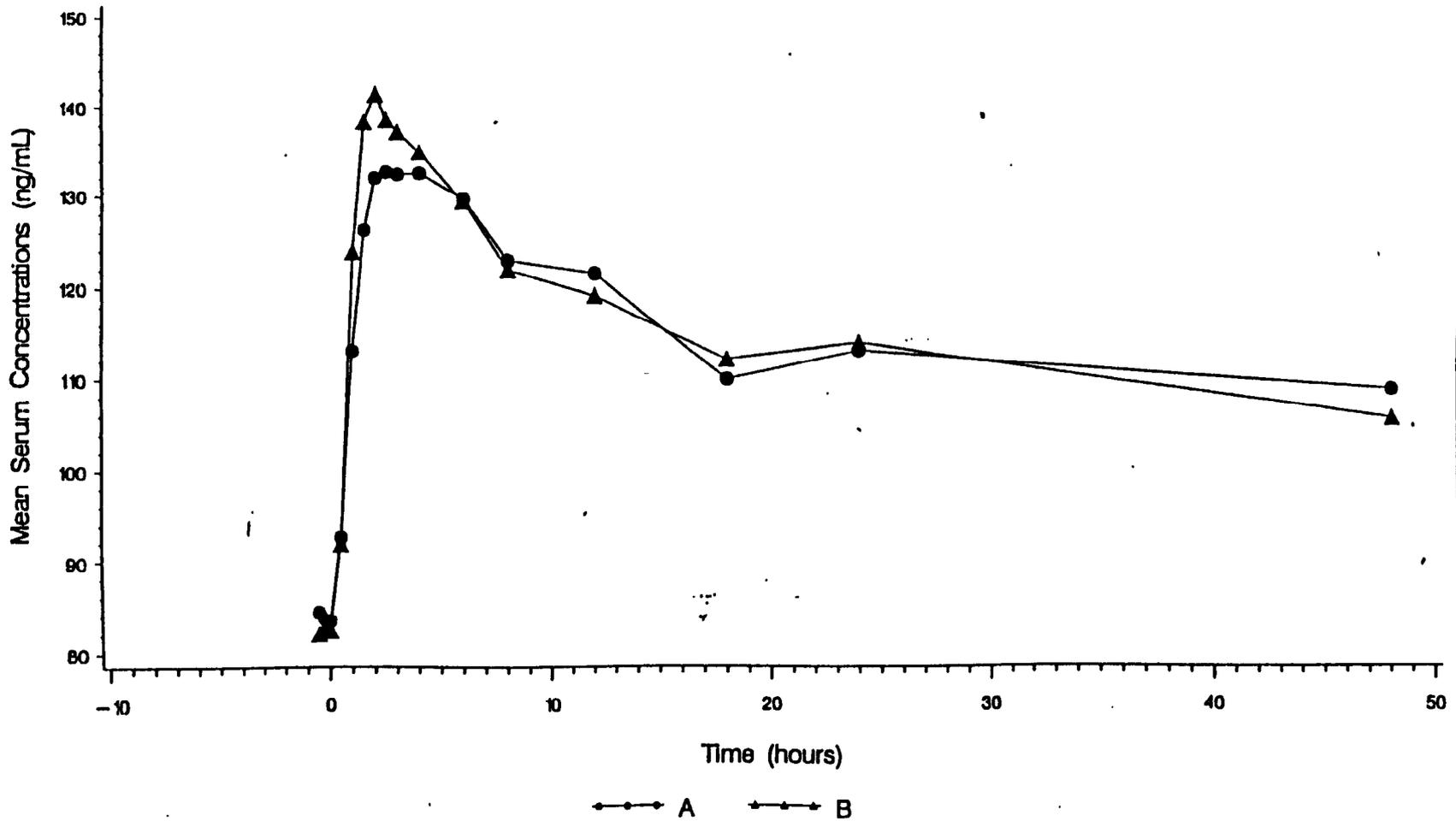
ml

FIGURE 1: MEAN L-THYROXINE PLASMA CONCENTRATION

LEVOTHYROXINE Na (LEVO-0054)

Total Dose: 500 ug (4x125ug Tablets), Study Type: Fasting

Mean L-thyroxine Serum Concentrations



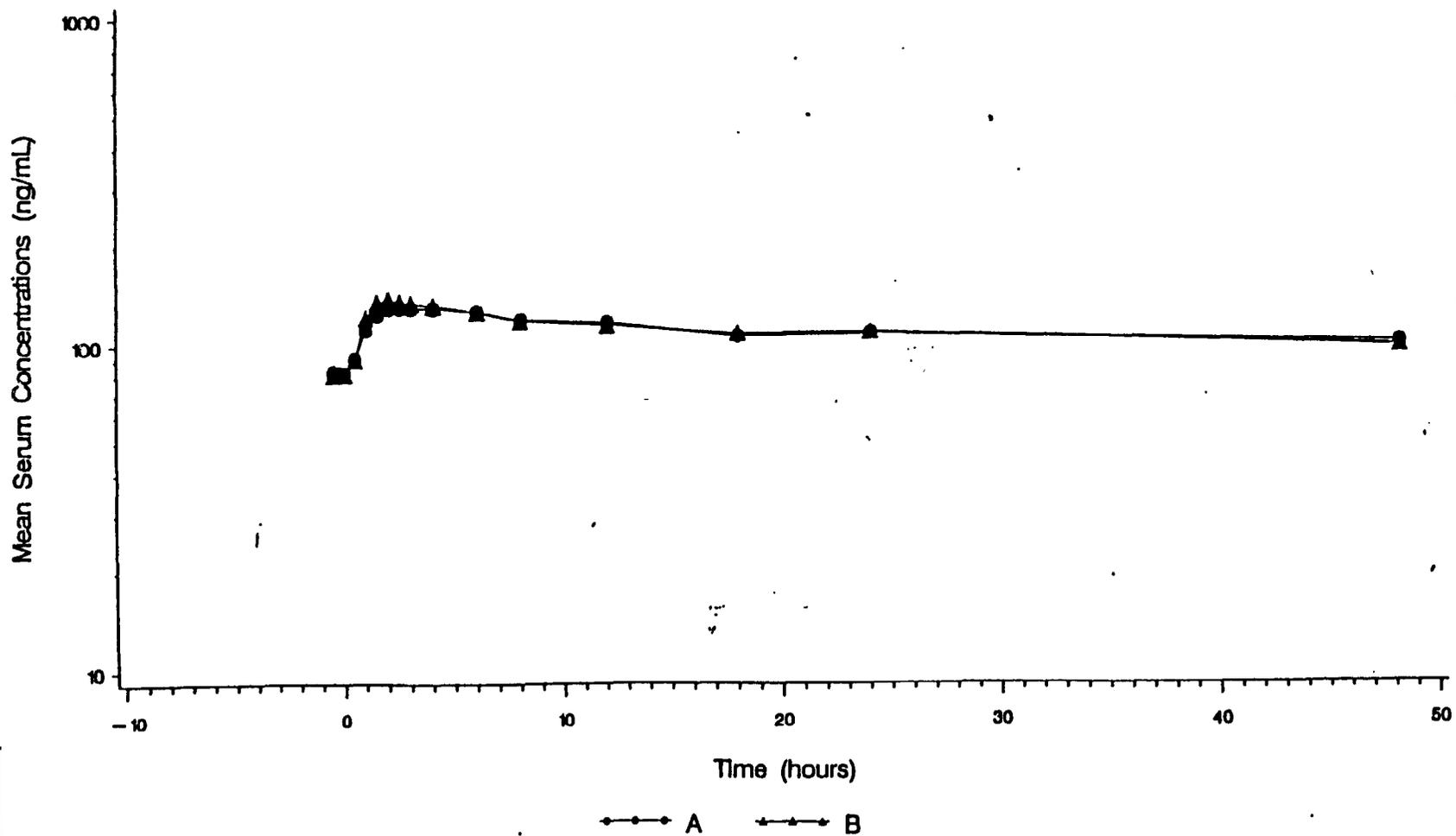
Treatment A is A (Levothyroxine Na--Mylan #R1H0750)

Treatment B is B (Levothyroxine Na--Jerome Stevens #003799)

LEVOTHYROXINE Na (LEVO-0054)

Total Dose: 500 ug (4x125ug Tablets), Study Type: Fasting

Mean L-thyroxine Serum Concentrations



Treatment A is A (Levothyroxine Na -- Mylan #R1H0750)

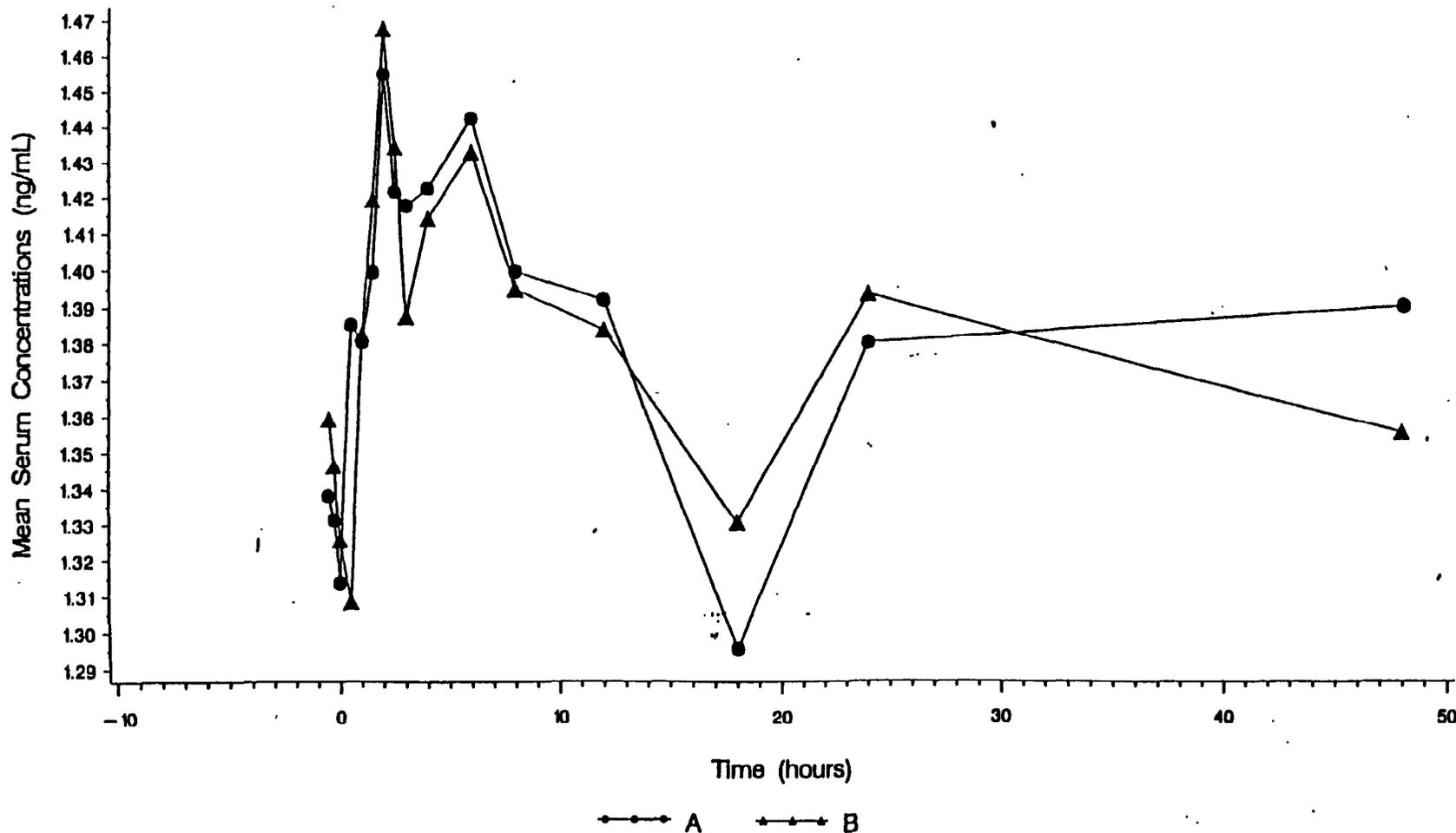
Treatment B is B (Levothyroxine Na -- Jerome Stevens #003799)

FIGURE 2: MEAN L-TRIIODOTHYRONINE PLASMA CONCENTRATION

LEVOTHYROXINE Na (LEVO-0054)

Total Dose: 500 ug (4x125ug Tablets), Study Type: Fasting

Mean L-triiodothyronine Serum Concentrations

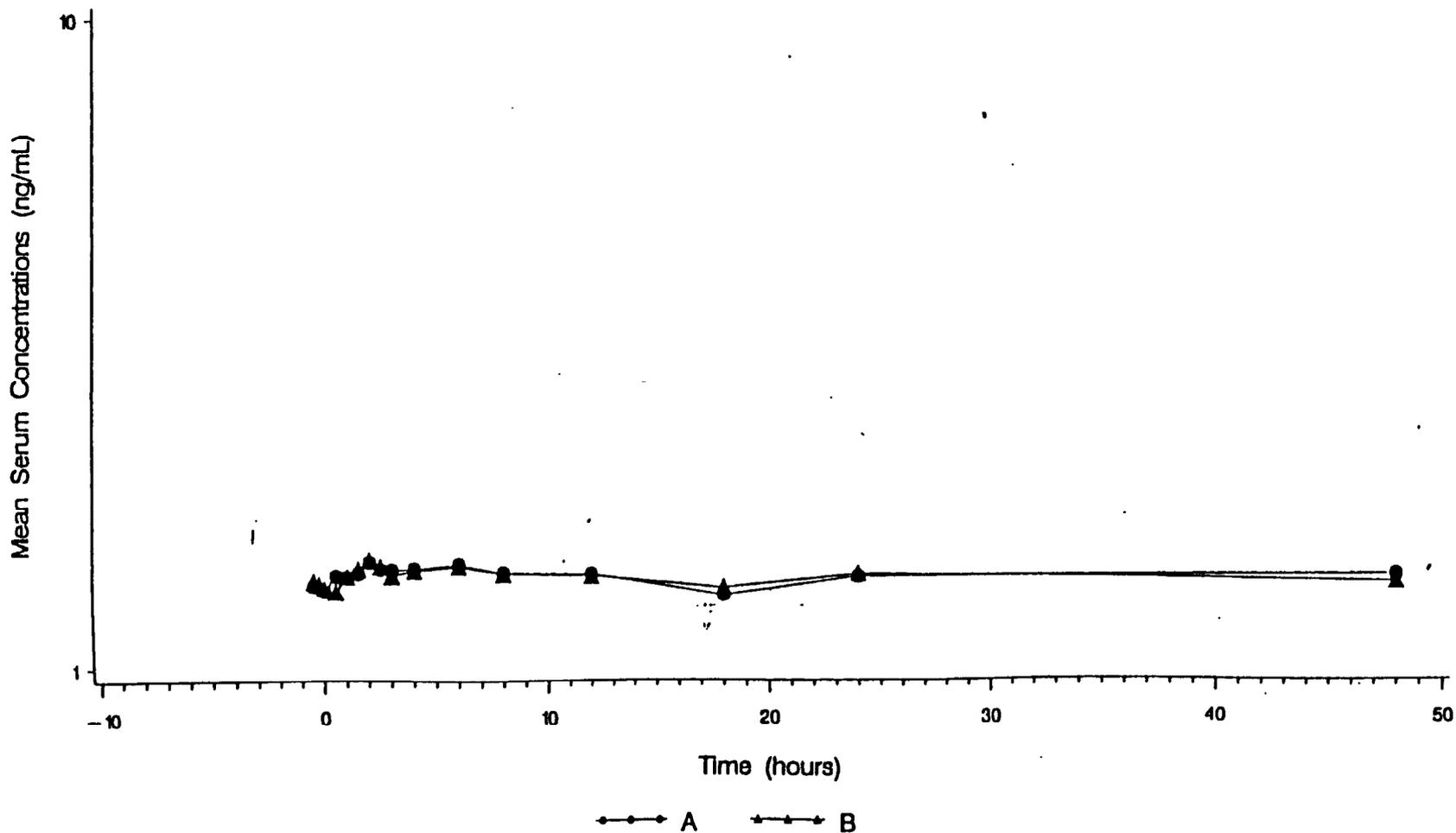


Treatment A is A (Levothyroxine Na—Mylan #R1H0750)

Treatment B is B (Levothyroxine Na—Jerome Stevens #003799)

LEVOTHYROXINE Na (LEVO-0054)

Total Dose: 500 ug (4x125ug Tablets), Study Type: Fasting
Mean L-triiodothyronine Serum Concentrations



Treatment A is A (Levothyroxine Na--Mylan #R1H0750)

Treatment B is B (Levothyroxine Na--Jerome Stevens #003799)

STATISTICAL ANALYSIS: L-THYROXINE

- A. Mean Data and Indices of Variance
- B. Analysis of Variance
- C. Confidence Intervals

LEVOTHYROXINE Na [LEVO-0054]
 L-thyroxine Serum
 Subject Concentration Profiles
 Mean Data Arranged by the Treatment Variable
 02/15/01

----- TREAT=A -----

Variable	Label	N	Mean	Std Dev	CV
CONC1	-0.50 hours	28	84.4335714	12.9586285	15.3477204
CONC2	-0.25 hours	28	83.7737857	11.0330018	13.1699931
CONC3	0.00 hours	28	83.5685714	11.6179345	13.9022773
CONC4	0.50 hours	28	92.7862857	15.7956797	17.0237224
CONC5	1.00 hours	28	113.4395000	19.7699923	17.4277851
CONC6	1.50 hours	28	126.6688929	22.7336749	17.9473226
CONC7	2.00 hours	28	132.5658214	22.3429560	16.8542357
CONC8	2.50 hours	28	133.2168929	17.7448070	13.3202379
CONC9	3.00 hours	28	132.9807500	17.1719863	12.9131369
CONC10	4.00 hours	28	133.1188929	18.0666846	13.5718411
CONC11	6.00 hours	28	130.2046429	17.6470567	13.5533237
CONC12	8.00 hours	28	123.4301786	15.7429042	12.7545017
CONC13	12.00 hours	28	122.0724643	17.8507505	14.6230771
CONC14	18.00 hours	28	110.4210000	18.7400559	16.9714601
CONC15	24.00 hours	28	113.5674643	14.1851251	12.4904832
CONC16	48.00 hours	28	109.3848571	14.0146814	12.8122683

----- TREAT=B -----

Variable	Label	N	Mean	Std Dev	CV
CONC1	-0.50 hours	29	82.1765172	11.2061855	13.6367248
CONC2	-0.25 hours	29	82.7102069	10.9442682	13.2320648
CONC3	0.00 hours	29	82.5163448	11.1537947	13.5170732
CONC4	0.50 hours	29	91.9954828	15.3218570	16.6550102
CONC5	1.00 hours	29	124.2998276	20.9983269	16.8932873
CONC6	1.50 hours	29	138.8592069	22.6167794	16.2875620
CONC7	2.00 hours	29	141.9549655	19.0201055	13.3986898
CONC8	2.50 hours	29	139.0825862	14.2662787	10.2574155
CONC9	3.00 hours	29	137.7755517	16.9335150	12.2906530
CONC10	4.00 hours	29	135.4695517	16.3611648	12.0773743
CONC11	6.00 hours	29	129.8892759	14.7962564	11.3914380
CONC12	8.00 hours	29	122.4049310	14.9137745	12.1839654
CONC13	12.00 hours	29	119.6311724	14.1365224	11.8167549
CONC14	18.00 hours	29	112.6303103	11.8383656	10.5108168
CONC15	24.00 hours	29	114.4698276	15.2541083	13.3258769
CONC16	48.00 hours	29	106.1336552	13.1778417	12.4162705

LEVOTHYROXINE Na [LEVO-0054]
 L-thyroxine Serum
 Noncompartmental Pharmacokinetics Parameters
 Mean Data Arranged by the Treatment Variable
 02/15/01

----- TREAT=A -----

Variable	N	Mean	Std Dev	CV
AUCL	28	5539.45	690.7812453	12.4702081
AUCI	0	.	.	.
CPEAK	28	142.5473571	18.7936993	13.1841794
TPEAK	28	3.0892857	1.2985289	42.0333047
KEL	0	.	.	.
HALF	0	.	.	.
LNAUCL	28	8.6123728	0.1220819	1.4175178
LNAUCI	0	.	.	.
LNCPEAK	28	4.9510938	0.1343674	2.7138925

----- TREAT=B -----

Variable	N	Mean	Std Dev	CV
AUCL	29	5536.77	645.3429096	11.6555783
AUCI	0	.	.	.
CPEAK	29	147.0871034	19.0878694	12.9772556
TPEAK	29	2.7241379	1.5617424	57.3297853
KEL	0	.	.	.
HALF	0	.	.	.
LNAUCL	29	8.6127783	0.1144646	1.3290988
LNAUCI	0	.	.	.
LNCPEAK	29	4.9832158	0.1261352	2.5312016

STATISTICAL ANALYSIS: L-THYROXINE

B. Analysis of Variance

LEVOTHYROXINE Na [LEVO-0054]
L-thyroxine Serum Variables
. 02/15/01

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SEQ	2	1 2
TREAT	2	A B
PER	2	1 2
SUB	30	01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

Number of observations in data set = 57

Group	Obs	Dependent Variables
0	0	AUCI KEL HALF LNAUCI
1	57	AUCL CPEAK TPEAK LNAUCL LNCPEAK

NOTE: Variables in each group are consistent with respect to the presence or absence of missing values.

LEVOTHYROXINE Na [LEVO-0054]
 L-thyroxine Serum Variables
 .02/15/01

General Linear Models Procedure

Dependent Variable: AUCL

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	31	22789560.9	735147.1	10.47	0.0001
Error	25	1755456.2	70218.2		
Corrected Total	56	24545017.1			
	R-Square	C.V.	Root MSE		AUCL Mean
	0.928480	4.784814	264.987		5538.09

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	1690520.0	1690520.0	24.08	0.0001
SUB(SEQ)	28	21023388.6	750835.3	10.69	0.0001
TREAT	1	21802.1	21802.1	0.31	0.5823
PER	1	53850.2	53850.2	0.77	0.3895

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1821254.3	1821254.3	25.94	0.0001
SUB(SEQ)	28	20792295.6	742582.0	10.58	0.0001
TREAT	1	19309.7	19309.7	0.27	0.6046
PER	1	53850.2	53850.2	0.77	0.3895

Tests of Hypotheses using the Type III MS for SUB(SEQ) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	1821254.34	1821254.34	2.45	0.1286

Parameter	Estimate	T for H0: Parameter=0	Pr > T	Std Error of Estimate
A VS B	-37.8459203	-0.52	0.6046	72.1699145