CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215809Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 7, 2022
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 215809
Product Name and Strength:	Ermeza (levothyroxine sodium)oral solution, 150 mcg/5 mL (30 mcg/mL)
Applicant/Sponsor Name:	Mylan Pharmaceuticals Inc. (Mylan)
OSE RCM #:	2021-1317-1
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD, RPh
DMEPA 1 Team Leader:	Sevan H. Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on April 6, 2022 for Ermeza. Division of General Endocrinology (DGE) requested that we review the revised container label and carton labeling for Ermeza (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Howard, C. Label and Labeling Review for Levothyroxine sodium oral solution (NDA 215809). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 FEB 17. RCM No.: 2021-1317.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CORWIN D HOWARD
04/07/2022 04:26:06 PM

SEVAN H KOLEJIAN
04/07/2022 04:28:33 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 6, 2022
To:	Linda Galgay Regulatory Project Manager **Division of General Endocrinology (DGE)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Charuni Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Names (established names):	ERMEZA (levothyroxine sodium)
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 215089
Applicant:	Mylan Pharmaceuticals, Inc.

1 INTRODUCTION

On June 30, 2021, Mylan Pharmaceuticals Inc. submitted for the Agency's review an Original New Drug Application for levothyroxine sodium oral solution. The application seeks the approval of levothyroxine sodium oral solution using the bioavailability study of Synthroid (levothyroxine sodium) Tablets as a clinical bridge. Therefore, the Sponsor is relying on the Agency's previous findings of safety and effectiveness for Synthroid (levothyroxine sodium) Tablets.

Levothyroxine sodium (T4) is indicated in adult and pediatric patients, including neonates for:

- Hypothyroidism: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.
- Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

This is a collaborative review from DMPP and OPDP. This review is written by the Division of Medical Policy Programs (DMPP) and OPDP in response to a request by on July 6, 2021 by the Division of General Endocrinology (DGE) to review the Applicant's proposed PPI and IFU for levothyroxine sodium oral solution.

2 MATERIAL REVIEWED

- Draft ERMEZA (levothyroxine sodium) PPI and IFU received on June 30, 2021, and received by DMPP and OPDP on March 29, 2022.
- Draft ERMEZA (levothyroxine sodium) Prescribing Information (PI) received on June 30, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 29, 2022.
- Approved comparator labeling TIROSINT-SOL (levothyroxine sodium) oral solution dated February 24, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MGs and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON W WILLIAMS
04/06/2022 07:35:16 AM

CHARUNI P SHAH
04/06/2022 03:56:35 PM

20 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHARUNI P SHAH
04/05/2022 02:26:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Memorandum

Date: March 15, 2022 **Date consulted:** July 6, 2021

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH

To: Division of General Endocrinology (DGE)

Drug: Levothyroxine sodium oral solution

Drug Class: Thyroid medication

NDA: 215809

Applicant: Mylan Pharmaceuticals, Inc

Subject: Pregnancy and Lactation Labeling to comply with Pregnancy and Lactation Labeling Rule (PLLR)

Indication: In adult and pediatric patients, including neonates, for:

- Hypothyroidism: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.
- Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

Limitations of Use:

- Not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients.
- Not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis.

Materials Reviewed:

- DPMH consult request dated July 6, 2021, in DARRTS (Reference ID: 4822226)

- Applicant's submission for NDA 215809, including draft labeling, dated June 30, 2021

Consult Question:
DGE requests DPMH's assistance with reviewing the applicant's Pregnancy and Lactation labeling subsections to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format. DPMH will ensure that the labeling language is consistent with current practices.

INTRODUCTION
On June 30, 2021, the applicant, Mylan Pharmaceuticals, Inc. (Mylan), submitted the original NDA 215809 application for levothyroxine sodium oral solution. DGE consulted DPMH on July 6, 2021, to provide input for appropriate labeling of the *Pregnancy* and *Lactation* subsections of levothyroxine sodium oral solution to comply with the PLLR.

BACKGROUND
Regulatory History
This 505 (b)(2) application is based on a single bioequivalence (BE) study that establishes a clinical bridge to Synthroid. Synthroid tablets, for oral use, NDA 021402 was approved on July 24, 2002. It is the drug relied upon for this NDA 215809, to be approved under 505(b)(2) with the same indications. Mylan has not performed clinical evaluations in patients due "to the wealth of efficacy and safety information that has already been established for levothyroxine in Hypothyroidism and Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression". No efficacy or safety studies were performed.

Drug Characteristics[1]
- Molecular weight is 798.85 g/mol (Daltons)(D).
- 99% bound to plasma proteins, including thyroxine- binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and thyroxine-binding albumin (TBA),
- Plasma half-life is about 6-7 days (in hypothyroidism it is 9-10 days).
- Oral bioavailability is 40%-80%

REVIEW
PREGNANCY
The applicant has not provided a review of literature or relevant cases from their pharmacovigilance database.
There are no animal studies conducted with levothyroxine during pregnancy. Previous DPMH literature reviews have not identified any risks.[2,3,4,5,6] Oral levothyroxine administered to

[1] Synthroid existing labeling of July 15, 2020
[2] Mastroyannis, Christos MD, Labeling review of Levolet (levothyroxine sodium) tablets, NDA 021137/S-002, in DARRTS and dated November 5, 2021, Reference ID: 4884144
[3] Sun, Wenjie MD, Labeling review of levothyroxine sodium oral solution, NDA 214047, in DARRTS and dated September 2, 2020, Reference ID: 4664627
[4] Mastroyannis, Christos MD, Labeling review of levothyroxine sodium injection, NDA 210632, in DARRTS and dated March 11, 2019, Reference ID: 4400668
[5] Spaulding, Jacqueline MD, Labeling review of Tirosint-SOL (levothyroxine sodium) oral solution, NDA 206977, in DARRTS and dated November 10, 2016, Reference ID: 4009468
[6] DPMH did not rely on data in any of the levothyroxine sodium NDAs or the agency's finding of safety and effectiveness for levothyroxine sodium to support labeling sections of this levothyroxine sodium oral solution NDA. Rather, the cross-reference to the levothyroxine sodium consults is included to avoid duplicating background information relevant to this class of products.

pregnant patients to maintain a euthyroid state have not reported increased rates of major birth defects, miscarriages, or adverse maternal or fetal outcomes.

LACTATION

The applicant has not provided a review of literature or relevant cases from their pharmacovigilance database.

There are no animal lactation studies that have been conducted with levothyroxine.

In LactMed, the "Summary of Use during Lactation" section notes the following:

> Levothyroxine is a normal component of human milk. Limited data on exogenous replacement doses of levothyroxine during breastfeeding indicate no adverse effects in infants. It appears that levothyroxine passes into milk poorly. If levothyroxine is required by the mother, it is not a reason to discontinue breastfeeding.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

The applicant has not provided a review of literature or relevant cases from their pharmacovigilance database.

There have been no animal studies conducted to evaluate the effects of levothyroxine on fertility. There is no evidence in the literature to suggest that levothyroxine adversely effects male or female fertility. Since there are no human data available on the effect of levothyroxine on male or female fertility Section 8.3, Females and Males of Reproductive Potential, will not be included in levothyroxine sodium oral solution labeling.

CONCLUSIONS

Levothyroxine sodium oral solution draft labeling has been edited to comply with the current practices for PLLR. DPMH revised labeling subsections 8.1 and 8.2 (see below).

DPMH refers to the final NDA action for final labeling.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHRISTOS MASTROYANNIS
03/16/2022 05:18:28 PM

TAMARA N JOHNSON
03/16/2022 06:32:31 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research
Office of New Drugs, Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:	July 06, 2021
From:	Ndidi Nwokorie, MD Medical Officer Division of Pediatrics and Maternal Health (DPMH) Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM) Office of New Drugs (OND)
Through:	Mona Khurana, MD, Pediatric Team Leader DPMH, ORPURM, OND
To:	Division of General Endocrinology (DGE) Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
NDA/BLA Number:	NDA 215809
Drug:	Levothyroxine Sodium Oral Solution
Applicant:	Mylan Pharmaceuticals, Inc.
Indication:	**Hypothyroidism**: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism. **Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression:** As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

Consult Request

DGE submitted a consult on July 06, 2021, requesting DPMH to provide pediatric labeling recommendations for Levothyroxine Sodium Oral Solution.

Brief Background

Mylan Pharmaceuticals Inc. submitted a New Drug Application (NDA) on June 30, 2021, seeking approval under the 505 (b)(2) pathway for Levothyroxine Sodium Oral Solution by establishing bioequivalence to Synthroid (levothyroxine sodium) Tablets, (NDA 021402) as the listed drug (LD). NDA 215809 is not subject to the Pediatric Research Equity Act (PREA) because this (b)(2) Applicant is not seeking a new dosage form, dosing regimen, indication, or route of administration for levothyroxine sodium. The LD is approved down to birth for the same indications the (b)(2) Applicant is seeking.

DPMH had previously provided recommendations to DGE to update class labeling for levothyroxine sodium drug products.[1] Based on these recommendations, DGE subsequently collaborated with DPMH to revise the LD labeling[2] and use the revised content in the LD labeling as a framework for developing pediatric labeling content for other levothyroxine sodium drug products for which labeling supplements had been submitted to the Agency and were under review.

DPMH participated in internal team meetings with DP from November 2021 to April 2022 and provided pediatric labeling recommendations for this product labeling consistent with those outlined in DPMH's October 2021 memorandum and with those previously implemented for the LD labeling. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the Applicant and may not fully reflect changes suggested here.

DPMH Pediatric MO Reviewer- Ndidi Nwokorie
DPMH Pediatric Team Leader- Mona Khurana
DPMH Division Deputy Director- John J. Alexander
DPMH RPM- Denise Johnson-Lyles

[1] Pediatric Review NDA 21137 in DARRTS 10/22/2021
[2] Primary Review NDA 21402 in DARRTS 03/04/2022

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NDIDI N NWOKORIE
03/14/2022 12:21:28 PM

MONA K KHURANA
03/14/2022 02:27:17 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 17, 2021
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	NDA 215809
Product Name, Dosage Form, and Strength:	Levothyroxine sodium oral solution [a] 150 mcg/5 mL (30 mcg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mylan Pharmaceuticals Inc. (Mylan)
FDA Received Date:	June 30, 2021 and December 22, 2021
OSE RCM #:	2021-1317
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD, RPh
DMEPA 1 Team Leader:	Sevan H. Kolejian, PharmD, MBA, BCPPS

[a] Mylan prefers proposed proprietary name, Ermeza*** for this product. We note that Mylan previously submitted the proposed proprietary name, Ermeza*** for review on June 30, 2021 for levothyroxine sodium Oral Solution under NDA 215809. However, DMEPA found the name unacceptable on September 28, 2021 because it could result in medication errors due to confusion with another product that is also under review. Thus, Mylan submitted the proprietary name, (b) (4), for review on December 7, 2021. At the time of this review, the proprietary name (b) (4) is being reviewed by DMEPA.

1 REASON FOR REVIEW

As part of the approval process for Levothyroxine sodium oral solution, the Division of General Endocrinology (DGE) requested that we review the proposed Prescribing Information (PI), instructions for use (IFU), patient Labeling (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

(b) (4)

We note that the proposed product in this NDA submission includes two oral syringes in a volumetric unit of measure, milliliters (mL) (b) (4)

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[b] Flint, Jason. Label and Labeling Review for levothyroxine sodium, oral solution (IND 141382). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 28. RCM No.: 2020-644.

(b) (4)

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The propose levothyroxine sodium oral solution is supplied as a bottle with cap containing the drug product and two oral dosing syringes to accommodate a range of doses. The two oral dosing syringes have a nominal capacity of 8 mL and 12.5 mL respectively. The oral dosing syringe with an 8 ml nominal capacity is intended to measure doses up to 5 mL in 0.1 mL increments and the oral dosing syringe with a 12.5 mL nominal capacity is intended to measure doses greater than 5 mL up to 10 mL in 0.2 mL increments (see figure below).

(b) (4)

During our preliminary review of the prescribing information (PI), DMEPA noted that the supplied oral dosing syringes does not correspond to all the intended levothyroxine sodium oral solution doses volume to administer. Thus, we were concerned that prescribers would not know what doses can be delivered with the proposed oral syringes, increasing the risk that a prescriber may prescribe a dose that does not match with the proposed syringes graduations. For example, if physician prescribes 12.5 mcg dose (0.416 mL), this volume cannot be measured with the proposed 5 mL oral syringe. This concern was communicated to the review team.

Subsequently, DGE send an information request (IR) to the Applicant requesting that the Dosage and Administration section of the PI be revised to include the volume of administration corresponding to the respective pediatric and adult dosing of your levothyroxine sodium oral solution[d]. To address Agency's IR, on December 22, 2022, the Applicant submitted revised proposed prescribing information, revising the section 2 of the PI to include General Principles of Dosing section which includes information about the dosing and the volume of administration using the dosing syringes included in the packaging. The section also includes a table that shows an example of dosing volumes in mL for the equivalent mcg dosages and clarifies how the volume of administration should be round up or down. We found the

[d] Hanan, E. Information Request for "NDA 215809 preliminary labeling comments" Message to Bradly, Peggy. Silver Spring (MD): FDA, CDER, OND, DGE (US); 2021 DEC 3.

proposed revisions are appropriate to help clinicians to determine the dosing and the appropriate volume of administration.

4 CONCLUSION & RECOMMENDATIONS

Our review evaluation of the proposed IFU identified areas of vulnerability that may lead to medication errors. We have provided recommendations below in Section 4.1 for the applicant. We ask that the Division convey the recommendations in its entirety to Mylan so that recommendations are implemented prior to approval of this NDA.

Our evaluation of the proposed PI, IFU, PPI, container label and carton labeling did not identify areas of vulnerability that may lead to medication errors. However, we note that the proprietary name placeholder "TRADENAME" is used throughout the labels and labeling. Once the proprietary name is found conditionally acceptable, the placeholder should be replaced with the proprietary name and submitted to the agency.

4.1 RECOMMENDATIONS FOR MYLAN PHARMACEUTICALS INC. (MYLAN)

We recommend the following be implemented prior to approval of this NDA:

1. General comment:
   The placeholder "Tradename" on container labels and carton labeling should be replaced with the proprietary name and submitted to the agency.

2. Instruction for use (IFU):
   a. The packaging contains two oral syringes, 5 mL and 10 mL. However, the proposed IFU does not contain any information about which oral syringe should user use to administer the prescribed dose. Add clear instruction in the IFU about how the patient or caregiver should select the appropriate oral syringe to measure the prescribed dose.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for levothyroxine sodium received on June 30, 2021, from Mylan Pharmaceuticals Inc. (Mylan), and the listed drug (LD).

Table 2. Relevant Product Information for levothyroxine sodium and the Listed Drug		
Product Name	levothyroxine sodium	Thyquidity[e] (levothyroxine sodium)
Initial Approval Date	N/A	November 30, 2020
Active Ingredient	Levothyroxine sodium	levothyroxine sodium
Indication	•Hypothyroidism: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism. •Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer. <u>Limitations of Use:</u> -Not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients -Not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis	• Hypothyroidism: As replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism. • Pituitary Thyrotropin (Thyroid-Stimulating Hormone, TSH) Suppression: As an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer. <u>Limitations of Use</u>: - Not indicated for suppression of benign thyroid nodules and nontoxic diffuse goiter in iodine-sufficient patients - Not indicated for treatment of hypothyroidism during the recovery phase of subacute thyroiditis
Route of Administration	Oral	Oral
Dosage Form	oral solution	Oral solution

[e] Thyquidity [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020/Nov/30. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214047s000lbl.pdf

.

Strength	150 mcg/5 mL (30 mcg/mL)	100 mcg/5 mL (20 mcg/mL)
Dose and Frequency		
How Supplied	oral solution, 150 mcg per 5 mL (30 mcg per mL) is a clear, colorless solution supplied in a 90 mL or 180 mL amber glass bottle with a child-resistant closure.	oral solution, 100 mcg per 5 mL (20 mcg per mL) is a clear, colorless to nearly colorless solution supplied in a 100 mL amber glass bottle with a child-resistant closure. *The pharmacy will provide a calibrated oral syringe to accurately measure the prescribed dose.*
Storage	Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from light. Store and dispense in original bottle. Use within 90 days of opening the bottle	Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature]. Protect from light. Store and dispense in original bottle. Use within 8 weeks of opening the bottle.
Container Closure	90 mL and 180 mL amber glass bottles.	100 mL amber glass bottle with a child-resistant closure.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 16, 2021 we searched for previous DMEPA reviews relevant to this current review using the terms, "levothyroxine sodium". Our search did not identify and relevant reviews. Additionally, we searched "IND 141382". Our search identified two previous reviews[f,g], and we considered our previous recommendations to see if they are applicable for this current review.

[f] Flint, Jason. Label and Labeling Review for levothyroxine sodium, oral solution (IND 141382). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 28. RCM No.: 2020-644.

(b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with postmarket medication error data, we reviewed the following levothyroxine sodium labels and labeling submitted by Mylan Pharmaceuticals Inc. (Mylan).

- Container label and carton labeling received on June 30, 2021 and December 22, 2021

- Instructions for Use received on June 30, 2021 and December 22, 2021 available from \\CDSESUB1\evsprod\nda215809\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use.pdf \\CDSESUB1\evsprod\nda215809\0006\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-clean-pdf.pdf

- Prescribing Information (Image not shown):
  - received on June 30, 2021 available from \\CDSESUB1\evsprod\nda215809\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text.pdf
  - Received on December 22, 2021 available from \\CDSESUB1\evsprod\NDA215809\0006\m1\us\114-labeling\draft\labeling

- Patient Labeling received on December 22, 2021 available from \\CDSESUB1\evsprod\NDA215809\0006\m1\us\114-labeling\draft\labeling

G.2 Label and Labeling Images

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CORWIN D HOWARD
02/17/2022 11:45:13 AM

SEVAN H KOLEJIAN
02/17/2022 01:53:56 PM

M E M O R A N D U M

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

DATE: 10/15/2021

TO: Division of General Endocrinology (DGE)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 215809

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

Novum Pharmaceutical Research Services, Las Vegas: The Office of Regulatory Affairs (ORA) inspected the site in February 2019, which falls within the surveillance interval. The inspection was conducted under the following submission: ANDA (b) (4).

Mylan, Morgantown: OSIS inspected the site in November 2018, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs (b) (4) and (b) (4).

The final classification for both inspections was No Action Indicated (NAI).

Therefore, based on the rationale described above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Novum Pharmaceutical Research Services, Inc.	3760 Pecos McLeod, Las Vegas, NV
Analytical	Mylan Pharmaceuticals, Inc.	3711 Collins Ferry Road, Morgantown, WV

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLA M FENTY-STEWART
10/15/2021 03:00:11 PM