CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214047Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approval

NDA 214047
Review 1

Drug Name/Dosage Form	Thyquidity (levothyroxine sodium) oral solution
Strength	2000 mcg/100 mL (20 mcg/mL)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	EMP Levo US B.V.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission, and amendments	Original submission: 1/31/2020 Amendments: 4/24/2020, 6/2/2020,6/17/2020, 6/19/20, 6/22/2020, 7/06/2020, 8/07/20, 9/02/20, 9/30/20, and 10/14/20	Quality modules 3, 1.14, and 1.11

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Substance	Daniel Jansen/ Suong Tran	Branch III/Division of New Drug API/Office of New Drug Products (ONDP)
Drug Product	Dan Berger / David J Claffey	Branch V/Division of New Drug Products III/ONDP
Process/ Facility	Allison Aldridge/Rose Xu	Branch II/ Office of Pharmaceutical Manufacturing Assessment (OPMA)
Microbiology	Amanda Bursik/ Erika Pfeiler	Division of Microbiology Assessment/OPMA
Regulatory Business Process Manager	Leeza Rahimi/ Hamet Toure	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch V/Division of New Drug Products III/ONDP
Environmental Analysis (EA)	Dan Berger / David J Claffey	Branch V/Division of New Drug Products III /ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Active	April20	LOA dated 10/28/2019
	III			Active	*	LOA dated 11/11/2019
	III			Active	*	LOA dated 10/22/2019

*Sufficient information provided in the NA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	127792	Levothyroxine sodium solution
ANDA	200343	Related to glycerin levels in Hydrocodone Bitartrate and Acetaminophen Oral Solution

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharm./Tox. – Limit for impurities and glycerin content	Completed	Acceptable	April 13, 2020	Dr. Parvaneh Espandiari

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 214047 is approval, which includes an acceptable recommendation for the facilities listed in the application.

II. Summary of Quality Assessments

A. Product Overview

The proposed 505(b)(2) application is for Thyquidity (levothyroxine sodium) oral solution, 2000 mcg/100 mL. This NDA references Synthroid (levothyroxine sodium) tablets as the listed drug (NDA 021402). Synthroid was approved in 2002. The established name for the proposed drug product is levothyroxine sodium oral solution. Consistent with the strength expression used for the listed drug, the strength of the proposed drug will be expressed in levothyroxine sodium content. Thyquidity is a clear, colorless to nearly colorless solution provided in a multiple-dose amber glass bottle with child resistant closure. Each mL of Thyquidity contains 20 mcg of levothyroxine sodium. An oral solution is proposed as it offers ease of administration to people having swallowing difficulty and flexibility in terms of dose adjustment. The dose will be measured and administered using a calibrated pharmacy provided oral syringe. The proposed product is for treatment of hypothyroidism and Pituitary TSH suppression (see below, proposed indication section).

The drug product should be stored at 20°C to 25°C (68°F to 77°F) in original bottle protected away from light. Excursions permitted between 15°C and 30°C (59°F and 86°F). The product needs to be used within 8 weeks of first opening.

Proposed Indication(s) including Intended Patient Population	Hypothyroidism and Pituitary TSH suppression
Duration of Treatment	See CDTL memo
Maximum Daily Dose	300 mcg
Alternative Methods of Administration	Not applicable

B. Quality Assessment Overview

Drug Substance

The drug substance is manufactured by (b) (4). The applicant provided reference to (b) (4) Type II DMF (b) (4) for all chemistry manufacturing and control (CMC) information related to the drug substance, levothyroxine sodium USP. The chemical

name for the drug substance is monosodium L-thyroxine hydrate. The molecular formula and molecular weight of the drug substance is respectively $C_{15}H_{10}I_4NNaO_4$. xH_2O and 798.85 g/mol (anhydrous). The drug substance is a light yellow to buff colored powder, hygroscopic, and slightly soluble in water. Dr. Daniel Jansen reviewed the CMC drug substance information provided in the DMF (b) (4) as well as in the NDA.

Dr. Jansen reviewed the drug substance information provided in the DMF (b) (4) as well in the NDA. Per drug substance reviewer, the proposed drug substance specification is consistent with the USP monograph for levothyroxine sodium and is adequate to control the quality of the drug substance used in drug product manufacturing. Based on stability data review, a retest period of (b) (4) months is granted for the drug substance, when stored (b) (4) Dr. Jansen's review concluded that the CMC information provided in the NDA and DMF (b) (4) is adequate to support the NDA. For additional details, please refer to Dr. Jansen's CMC reviews dated 5/28/2020 and 10/8/2020 (addendum) in Panorama.

Drug Product

Thyquidity is a clear, colorless to nearly colorless solution provided in a multiple-dose 150 mL amber glass bottle sealed with a child resistant closure. Each mL contains 20 mcg levothyroxine sodium, (b) (4) glycerin, (b) (4) citric acid, and (b) (4) methyl paraben in purified water. Sodium hydroxide is added (b) (4). The composition of the proposed commercial product is the same as the one used in pilot and pivotal BE studies. The excipients used in the drug product are compendial grade.

Dr. Berger reviewed the drug product information including drug product composition, drug product specification including assay and limits proposed for impurities, excipient information, analytical methods, container closure system, compatibility information, stability data, and environmental assessment (EA). Dr. Berger granted the exemption for environmental assessment per 21 CFR 25.31.

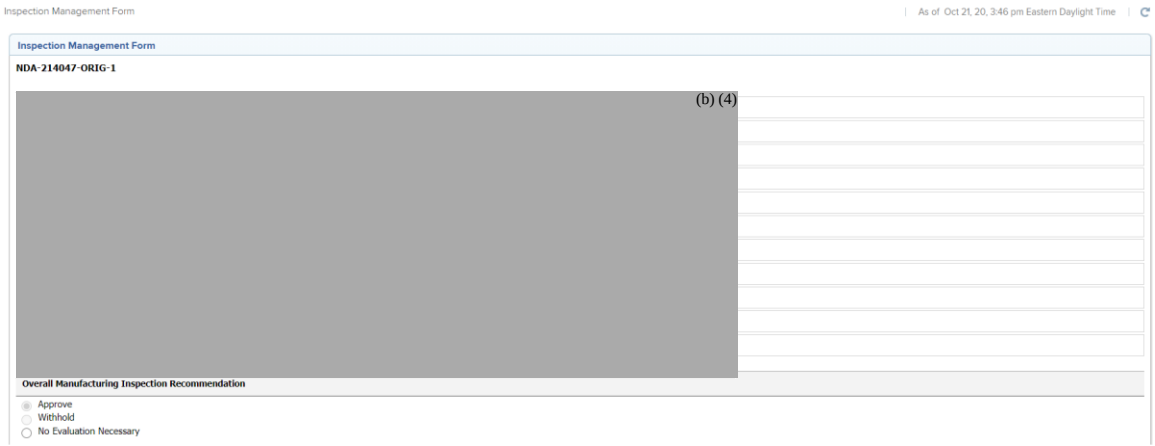
The maximum daily dose for this product is 300 mcg per day. The maximum daily dose will contain (b) (4) glycerin. Regarding the acceptability of glycerin level in the maximum daily dose, the drug product reviewer, Dr. Dan Berger consulted Pharm./Tox. reviewer and concluded that the proposed levels of glycerol is not a safety concern.

The drug product is tested for appearance, identity, pH, assay of active, impurities, methyl paraben content, deliverable volume, uniformity of dosage units, closure integrity, microbiological contamination testing (USP <60>, <61>, <62> , and <1111>) and antimicrobial effectiveness testing (USP <51>). Dr. Dan Berger reviewed the chemistry testing aspects of the drug product specification and Dr. Amanda Bursik reviewed the microbiological contamination controls part of the product specification. The microbiology and drug product reviewers concluded that the proposed drug product specification is adequate to support the NDA. For details, please refer to Dr. Berger's drug product review dated 10/1/20 and Dr. Bursik's review dated 6/15/2020 in Panorama.

The application contains 18 months of long-term stability data (25°C/60% RH), 12 months of intermediate storage stability data (30°C/65% RH), 8-week in-use stability data, and 6 month accelerated stability data (40°C/65% RH) for 3 primary stability batches manufactured at commercial scale (b) (4). Based on available stability data, an expiration period of 18 months is granted for the product, when stored at 20°C to 25°C (68°F to 77°F) in commercial packaging. An in-use period of 8 weeks is granted for the product after the first use. Dr. Berger also completed CMC labeling review for this NDA. Dr. Berger's overall recommendation for this NDA is adequate. Please refer to the Dr. Berger's drug product and labeling reviews dated 10/1/20 in panorama for additional information.

Manufacturing Process and Facility: Dr. Allison Aldridge reviewed the manufacturing process controls, batch record, and facility compliance information . The drug product manufacturing process, and the packaging system used to manufacture the drug product used in pilot and pivotal BE studies is the same as that proposed for commercial use. The manufacturing process involves (b) (4), (b) (4)

The overall manufacturing inspection recommendation (OMIR) from the Office of Process Manufacturing Assessment (OPMA) for this NDA is approve. The Panorama screen shot of the facility assessment recorded on 10/20/2020 is shown below. Dr. Aldridge's review concluded that the process and facility information in the NDA is adequate. For additional details, please refer to Dr. Aldridge's process/facility review in Panorama dated 10/15/2020.



OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process/facility, labeling, and microbiology sections of the NDA. The OPQ overall recommendation for NDA *214047 is approval.*

Muthukumar Ramaswamy, Ph.D. 10/21/2020

Application Technical Lead Name and Date

Muthukumar Ramaswamy

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Amendment to NDA 214047 Executive Summary

This amendment contains updated Quality Review Team table. Dr. Vidya Pai performed secondary review for process/facility instead of Dr. Rose Xu as identified in the cover page. Updated list is as follows:

Quality Review Team

Discipline	Reviewer/Secondary	Branch/division
Drug Substance	Daniel Jansen/ Suong Tran	Branch III/Division of New Drug API/Office of New Drug Products (ONDP)
Drug Product	Dan Berger / David J Claffey	Branch V/Division of New Drug Products III/ONDP
Process/ Facility	Allison Aldridge/Vidya Pai	Branch II/ Office of Pharmaceutical Manufacturing Assessment (OPMA)
Microbiology	Amanda Bursik/ Erika Pfeiler	Division of Microbiology Assessment/OPMA
Regulatory Business Process Manager	Leeza Rahimi/ Hamet Toure	Branch I/Regulatory Business Process Management I
Application Technical Lead	Muthukumar Ramaswamy	Branch V/Division of New Drug Products III/ONDP
Environmental Analysis (EA)	Dan Berger / David J Claffey	Branch V/Division of New Drug Products III /ONDP

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Inadequate

The Prescribing Information does not comply with regulatory requirements from a CMC perspective. Deficiencies to be addressed are listed below (see Items for Additional Assessment).

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Thyquidity	Adequate (listed as Tradename)
Established name(s)	levothyroxine sodium	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	100 mcg per 5 mL (20 mcg per mL) in 100 mL bottles, oral solution	Inadequate. Change to: 2,000 mcg per 100 mL.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	NA	NA

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Oral solution	Adequate
Strength(s) in metric system	100 mcg per 5 mL (20 mcg per mL)	Inadequate. Change to: 2,000 mcg per 100 mL.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	levothyroxine sodium	Adequate, salt name is consistent with RLD Synthroid.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Clear, colorless to nearly colorless solution	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME (levothyroxine sodium oral solution)	Adequate
Dosage form(s) and route(s) of administration	100 mcg per 5 mL (20 mcg per mL)	Inadequate. Change to: 2,000 mcg per 100 mL.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	levothyroxine sodium	Adequate, salt name is consistent with RLD Synthroid.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	citric acid monohydrate, glycerin, methylparaben sodium, sodium hydroxide and purified water.	Adequate
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	Thyroid hormone	Adequate
Chemical name, structural formula, molecular weight	L-3,3',5,5'-tetraiodothyronine sodium salt, $C_{15}H_{10}I_4NNaO_4 \cdot H_2O$, 798.85.	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Not present	Inadequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Oral solution	Adequate
Strength(s) in metric system	100 mcg per 5 mL (20 mcg per mL)	Inadequate. Change to: 2,000 mcg per 100 mL.
Available units (e.g., bottles of 100 tablets)	100 mL amber glass bottle	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	clear, colorless to nearly colorless solution, NDC XXXXX-XXX-XX	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Protect from light. Store and dispense in original bottle.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at room temperature 20° to 25°C (68° to 77°F)	Inadequate, °C and °F should be added after each number.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	Not present	Inadequate. Caps are child-resistant and (b) (4).

1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Not present	Inadequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

NA (no quality information is included in the Patient Counseling Information).

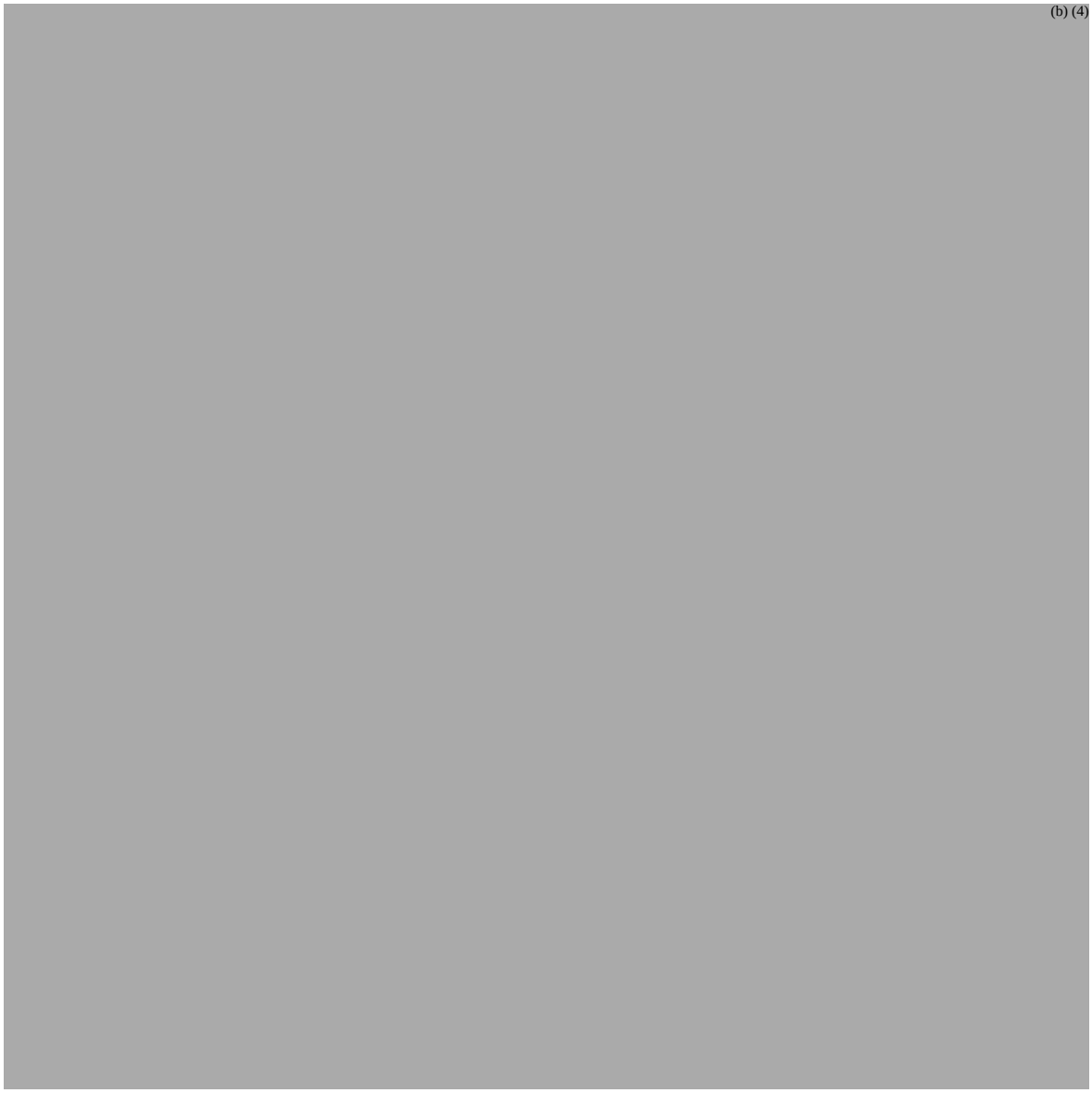
3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

(b) (4)


(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Bottle and Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	TRADENAME (levothyroxine sodium oral solution)	Adequate
Dosage strength	100 mcg per 5 mL (20 mcg per mL)	Inadequate. Change to: 2,000 mcg per 100 mL.
Route of administration	Oral Administration Only	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	levothyroxine sodium	Adequate, salt name is consistent with RLD Synthroid.
Net contents (e.g. tablet count)	100 mL	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	NDC XXXXX-XXX-XX	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature 20°C to 25°C (68°F to 77°F)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Bottle and Carton Labeling
Name of manufacturer/distributor	Distributed by:	Inadequate. No name is provided.
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: *Inadequate*

The container labels do not comply with regulatory requirements from a CMC perspective. Deficiencies to be addressed are listed below (see Items for Additional Assessment).

ITEMS FOR ADDITIONAL ASSESSMENT

List of labeling deficiencies:

1. Dosage strength is not listed as strength per total volume in Highlights and Sections 3, 11 and 16.
2. Important chemical or physical properties of the drug substance are not listed in Section 11.
3. The storage conditions in section 16 are not consistent with USP controlled room temperature language.
4. Information about child-resistant packaging is not listed in section 16.
5. The name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer is not provided in Section 17.

List of container deficiencies:

1. Dosage strength is not listed as strength per total volume on the bottle and carton labeling.
2. The name of a manufacturer/distributor has not been provided.

Overall Assessment and Recommendation: Deferred

From the ONDP perspective, this application is not recommended for approval per 314.125(b)(6) until the deficiencies are satisfactorily resolved in a subsequent resubmission (see the List of Deficiencies).

Primary Labeling Assessor Name and Date:

Dan Berger September 30, 2020

Secondary Assessor Name and Date (and Secondary Summary, as needed):

David Claffey September 30, 2020

Dan Berger

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David Claffey

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	214047
Assessment Cycle Number	01
Drug Product Name/ Strength	Levothyroxine Sodium Oral Solution/100 mcg/5 mL
Route of Administration	Oral
Applicant Name	EMP Levo US B.V.
Therapeutic Classification/ OND Division	DMEP
Manufacturing Site	(b) (4)
Method of Sterilization	N/A for nonsterile products

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original Submission	**1/31/2020**
IR Response	**6/2/2020**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This NDA is for a combination product, levothyroxine sodium oral solution, which is intended for use in patients with hypothyroidism and pituitary TSH suppression who have difficulty swallowing capsules and tablets. The drug product consists of an aqueous solution of Levothyroxine Sodium (100 mcg/5 mL) in a multi-dose amber glass bottle (b) (4) (b) (4). One filing IR was issued on 3/9/2020, prior to the 74 day letter, requesting BCC testing information. This IR is placed under Section P.2.5 in the template below. For additional sections affected by the IR, apart from P.2.5, only the applicant responses are listed.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed):

None

Supporting Documents: N/A

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Amanda Buskirk

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Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 6/15/2020 08:32:48AM
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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	NDA 214047
Drug Product Name	Levothyroxine Sodium Oral Solution
Strengths	100 mcg/5 mL
Dosage Form	Solution
Administration Route	Oral
Indication	Hypothyroidism
Applicant Name	EMP Levo US B.V.

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

The multi-dose drug product is an aqueous (clear, colorless to nearly colorless liquid) solution of 100 mcg Levothyroxine Sodium per 5 mL, filled in 100-mL amber glass bottles with a child-resistant, (b) (4) cap, (b) (4) (b) (4) (b) (4). The drug substance (b) (4) formulation includes glycerin.

The drug substance manufacturing facility has experience with the drug substance as well as an acceptable inspectional history. The drug product manufacturing facility has never been inspected by FDA.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
0001 (1) Original Submission	01/31/2020
0007 (7) Micro IR Response	06/02/2020
0009 (9) Drug Product IR Response	06/17/2020
0010 (10) Manufacturing IR Response	06/19/2020
0015 (15) Quality Information	09/02/2020
0017 (17) Manufacturing IR Response	09/30/2020
0018 (18) Manufacturing IR Response	10/13/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A, first review cycle

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

1. Post-Approval Commitments and Lifecycle Management Considerations

Postmarketing commitments (PMC)?	No
Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Approve - Based on Previous History
			Other 704(a)(4) assessment adequate

II. Drug Product Manufacturing

1. Batch Formula

Assessment: Adequate

The drug product is packaged in 100-mL amber glass bottles with a (b) (4) child-resistant, (b) (4) cap (b) (4) (b) (4). There are no overages proposed for the drug product (b) (4) .

The drug substance and preservative amounts are adjusted for water and residual solvents and purity.

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/s/

MUTHUKUMAR RAMASWAMY
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