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APPLICATION NUMBER:

215809Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA Memorandum

Application Number*:	215809
Supporting Document Number/s:	1
CDER Receipt Date:	06/30/2021
Sponsor:	Mylan Pharmaceuticals Inc.
Product:	Levothyroxine Sodium 150 µg/5 mL Oral Solution
Pharmacologic Class:	Thyroid hormone
Indication:	To establish a euthyroid state in patients with hypothyroidism
Therapeutic area:	Endocrinology, Diabetes, and Metabolism
Review Division:	Division of General Endocrinology
Reviewer:	Dongyu Guo, Ph.D.
Supervisor/Team Leader:	David Carlson, Ph.D.
Division Deputy Director:	C. Lee Elmore, Ph.D.
Project Manager:	Linda Galgay
Purpose of Review:	Other NDA memo
Alternative Assays:	Click here to enter text.
Reviewer Completion Date:	March 16, 2022

Template Version: May 23, 2019

Executive Summary

No nonclinical studies were submitted or required to support this 505(b)(2) NDA for Levothyroxine Sodium 150 µg/5 mL Oral Solution. The Applicant is relying on the Agency's previous findings of safety for the listed drug, Synthroid (NDA 021402), to satisfy the nonclinical requirements for this application. The drug formulation contains no novel excipients, and all present excipients are below the levels contained in previously approved drug products as listed in the FDA's Inactive Ingredient Database. Based on the available information, there are no safety concerns for the proposed formulation and this NDA is approvable from a Pharmacology/Toxicology perspective.

Drug information

Levothyroxine Sodium 150 µg/5 mL Oral Solution is supplied in a 90 mL or 180 mL amber glass bottle with child-resistant (b) (4) cap with (b) (4). Two Oral Dosing Syringes (5 mL an d10 mL) are included in the drug product. The maximum daily dose is 300 µg.

The drug formulation contains no novel excipients (Table 1). There are no safety concerns of impurities.

Table 1. Composition of Levothyroxine Sodium 150 µg/5 mL.

Ingredients	Pharmaceutical Funtion	mg/mL	Maximum Daily Exposure (MDE)	MDE in FDA IID
Levothyroxine Sodium	Active	0.03	300 µg	
Glycerin	(b) (4)			31536 mg
Edetate Disodium				360 mg
Purified Water				

Reviewer's comment: High amounts of glycerin has been used in FDA approved drugs (See the following excerpt from NDA 214047 Pharm/Tox review by Dr. Parvaneh Espandiari).

"Levothyroxine Sodium Oral Solution contains glycerol (b) (4). At the expected maximum recommended clinical dose (approximately 120 mcg in an 8 Kg child, 300 mcg in adults) the amount of glycerol administered is (b) (4) per day, respectively. As per the latest FDA IID update (July 28, 2020), glycerol maximum daily exposure is 31536 mg. Glycerol is generally recognized as safe (GRAS) and was well tolerated in animal studies, with the only effect being limited to local irritating effects in the gastrointestinal tract in short term rat and dog studies (lowest dose 2,800 and 5,600 mg/kg/day, respectively), likely due its hygroscopic and osmotic effects.
Glycerol was not genotoxic and was not carcinogenic in 2-year dietary studies in rats (up to 10,000 mg/kg/day) and mice. In development and reproduction studies, no effects on fertility and reproductive performance were observed in a two-generation study with glycerol administered by gavage at doses up to 2000 mg/kg/day. No maternal toxicity or teratogenic effects were seen in the rat, mouse or rabbit up to the highest dose tested (1180 mg/kg/day)[1,2].

In addition, similar or higher amounts of glycerol are present in FDA approved drug products for infants (Orfadin and Ravicti), children and adult (Hydrocodone Bitartrate and Acetaminophen Oral Solution (ANDA 200343, the right of reference letter was provided). Based on few published studies in infants, vomiting was the only reported adverse event related to the administration of glycerol via a nasogastric tube[3,4]. Oral doses of glycerol of 10 grams or more have been reported to cause headache, upset stomach and diarrhea (Orfadin label).”

Furthermore, DPMH assessed the safety of the glycerol content of levothyroxine sodium oral solution administered to young patients, particularly neonates. DPMH recommended inclusion of pediatric use information in labeling for the drug (NDA 214047, DARRTS 12/08/2020).

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/

DONGYU GUO
03/21/2022 07:44:28 AM

DAVID B CARLSON
03/21/2022 09:31:28 AM
Nonclinical approval recommendation