CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202231Orig1s000

CHEMISTRY REVIEW(S)

NDA 202231

Levothyroxine Sodium
for Injection

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: APP Pharmaceuticals, LLC.
1501 E. Woodfield Rd.
Suite 300
E. Schaumburg, IL 60173

Indication: Levothyroxine sodium for injection is indicated to treat (b) (4) (b) (4) myxedema coma.

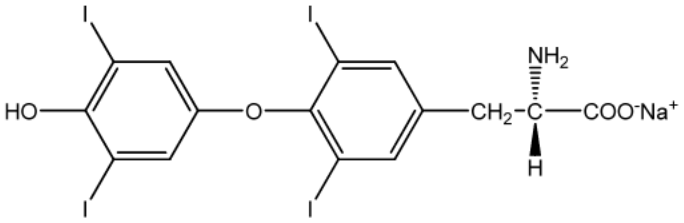
Presentation: Levothyroxine sodium for injection is packaged in single-use amber glass vials closed with a 20 mm gray (b) (4) rubber lyophilization stopper and capped with an aluminum crimped flip cap seal available in three dosage strengths: 100 mcg/vial, 200 mcg/vial and 500 mcg/vial.

Establishments Evaluation Report (EER) Status: **Acceptable**

Consults:	EA –	Acceptable
	Statistics –	N/A
	Methods Validation –	Not requested
	Biopharm –	N/A
	Microbiology –	Acceptable
	Pharm Toxicology –	N/A

Original Submission:	August 30, 2010
Re-submissions:	N/A
Post-Approval CMC Agreements:	None at this time.

Drug Substance
Levothyroxine sodium ($C_{15}H_{10}I_4NNaO_4$; MW = 798.85) is a light yellow to buff-colored, odorless, hygroscopic powder. It is stable in dry air but may assume a slight pink color upon exposure to light. It is very slightly soluble in water and slightly soluble in alcohol. Levothyroxine sodium is manufactured in the optically active L-form and has the following structure:



The drug substance specifications meet all requirements of the current USP monograph for levothyroxine sodium (updated Aug 1, 2008) with the addition of description, residual solvents, bioburden and bacterial endotoxins. All impurities and their limits are the same as listed in the USP monograph.

Information for the drug substance is provided in the (b) (4) DMF (b) (4) and is incorporated by reference herein. A copy of the letter of authorization to reference DMF (b) (4) has been provided. The DMF was reviewed by J. Leginus on Feb 11, 2011 and found to be adequate. The retest period for the drug substance is set at (b) (4) (b) (4)

Drug substance is satisfactory

Drug product

The drug product, levothyroxine sodium for injection, is a sterile, lyophilized powder consisting of the active ingredient, synthetic levothyroxine sodium, and the excipinets dibasic sodium phosphate, heptahydrate, USP; mannitol, USP; and sodium hydroxide, NF. Levothyroxine sodium for injection is packaged in single-use amber glass vials available in three dosage strengths: 100 mcg/vial, 200 mcg/vial and 500 mcg/vial. The manufacturing process for the drug product involves (b) (4)

The proposed release specifications include description, reconstitution time, visual inspection, pH, (b) (4) uniformity of dosage units, instrumental color, identity (HPLC), assay (HPLC), individual and total impurities (HPLC), (b) (4) container/closure integrity, particulate matter, sterility and bacterial endotoxin. All noncompendial regulatory methods have been validated.

(b) (4) Also, amber glass vials are used as the primary packaging material, which have been shown to adequately protect the lyophilized drug product from degradation due to light.

The applicant has provided only 6 months of real time (25°C/60% RH) and accelerated (40°C/75% RH) stability data for the three strengths of the drug product in stoppered and sealed vials. Results from stability studies show that the drug product remains

stable through 6 months under both conditions. In-use results show that drug product reconstituted with the recommended reconstitution diluent (0.9% sodium chloride injection, USP) remains stable for up to 4 hours at room temperature following dissolution, which supports the drug product label statement of "Use immediately after reconstitution". Based on these data, and following the recommendations outlined in ICH Q1E Evaluation of Stability Data, a shelf-life of 12 months is granted for levothyroxine sodium for injection when stored at controlled room temperature (20°C – 25°C).

Drug product is satisfactory

Overall Conclusion:

The NDA is recommended for Approval from the standpoint of chemistry, manufacturing and controls.

Ali Al-Hakim, Ph.D.
Branch Chief, Division III
ONDQA/CDRR/FDA

(b) (4)

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/s/

ALI H AL HAKIM
04/29/2011

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