CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202231Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DOCKET ALARM

Find authenticated court documents without watermarks at docketalarm.com.

CLINICAL PHARMACOLOGY REVIEW

NDA	202-231
Submission Dates	August 30, 2010 and December 20, 2010
Brand Name	*To be determined*
Generic Name	Levothyroxine sodium
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Sally Y. Choe, Ph.D.
OCP Division	Clinical Pharmacology 2 (HFD 870)
OND Division	Metabolism and Endocrinology Products (HFD 510)
Sponsor	APP Pharmaceuticals
Formulation; Strengths	Intravenous injection; 100, 200, and 500 µg/vial
Relevant IND	101,385
Indications	Treat myxedema coma (b) (4)

Table of Contents **Page**

1 Executive Summary

The sponsor is currently the sole supplier of levothyroxine sodium injection (200 and 500 µg/vial) to treat hypothyroid patients.

The Food and Drug Administration (FDA) categorized levothyroxine sodium injection a "Marketed Unapproved Drug," thus requiring a New Drug Application (NDA) submission and an approval in order to continue marketing the product. The sponsor received such an FDA Warning Letter on December 18, 2006. In compliance with the requirement, the sponsor submitted a 505(b)(2) NDA for their levothyroxine sodium injection without conducting any clinical studies to seek an approval for the indications of the treatment of myxedema coma, (b) (4) The sponsor relies only on published literature to support this NDA.

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

1.1 Recommendations
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 202-231's Clinical Pharmacology data and finds it acceptable.

1.2 Post Marketing Requirement or Post Marketing Commitment
None.

1.3 Summary of Important Clinical Pharmacology Findings
Although the sponsor did not conduct any study to demonstrate the in vivo bioavailability of their levothyroxine sodium injection and there is no FDA-approved levothyroxine sodium injection for the sponsor to refer, the requirement of in vivo bioavailability data for the sponsor's levothyroxine sodium injection may be waived for good cause so as to protect the public health per the CFR Section 320.22(e), since levothyroxine sodium injection is a medically necessary drug and is intravenously administered.

The review team mulled over the need of relative bioavailability information between intravenous levothyroxine sodium injection and oral levothyroxine sodium product so as to help clinicians transition patients from intravenous to oral dosing. For myxedema coma patients, the need for this relative bioavailability information is not as critical since:

- In clinical practice, it is generally understood that the intravenous dose is typically 50% of the oral dose. Therefore, clinicians can follow this practice when initiating oral levothyroxine.
- In general, when initiating oral levothyroxine, it is standard of care to reassess a patient clinically and with laboratory data at a minimum of 6 weeks after the drug is started. Therefore, unless a patient did not follow-up with their clinician, it would be unlikely that a patient would remain at a suboptimal oral dose for an extended period of time.

Thus, the relative bioavailability information between intravenous levothyroxine sodium injection and oral levothyroxine sodium product is "nice to have" and not "need to have" for myxedema coma patients. However, this relative levothyroxine bioavailability information may be critical for other indications such as hypothyroid patients who temporarily cannot take oral levothyroxine sodium products and have to be transitioned to intravenous administration.

Upon intravenous administration, levothyroxine rapidly distributes to tissues. Levothyroxine is more than 99% plasma protein bound, which protects the hormone from metabolism and excretion as well as resulting in a long half-life in the systemic circulation (about 6 – 8 days for euthyroid patients and 9 – 10 days for myxedema patients). The major pathway of thyroid hormone metabolism is via sequential deiodination. Thyroid hormones are primarily eliminated by the kidneys.

Both published mechanistic and clinical studies support the proposed intravenous levothyroxine sodium initial loading dose of 300 – 500 µg and maintenance dose of 50 – 100 µg once daily for myxedema coma.

_____
S.W. Johnny Lau, R.Ph., Ph.D.
OCP/DCP2

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

FT signed by Sally Y. Choe, Ph.D., Team Leader, 5/ /11

An Office Level Clinical Pharmacology Briefing for NDA 202-231 was conducted on April 29, 2011; participants included N. Lowy, D. Roman, A. Rahman, G. Burckart, L. Lesko, H. Ahn, D. Abernethy, L. Galgay, C. Sahajwalla, L. Jain, C. Shukla, J. Leginus, A. Agrawal, Z. Li, L. Zhao, K. Reynolds, R. Jain, I. Zadezensky, S. Naraharisetti, A. Khandelwal, Y. Mulugeta, J-E Lee, J. Bishai, S. Choe, and J. Lau.

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

2 Question-Based Review

The sponsor did not conduct any clinical pharmacology study and they relied only on published literature to support NDA 202-231.

2.1 Bioavailability Requirement

What is the requirement for the bioavailability of levothyroxine sodium injection?

Regulatory Requirement

Per the Code of Federal Regulation (CFR) 320.21 "Requirements for submission of bioavailability and bioequivalence data."

(a) Any person submitting a full new drug application to the Food and Drug Administration (FDA) shall include in the application either:

(1) Evidence measuring the in vivo bioavailability of the drug product that is the subject of the application; or

(2) Information to permit FDA to waive the submission of evidence measuring in vivo bioavailability.

The sponsor does not have any in vivo bioavailability data for their levothyroxine sodium injection and by submitting the literature data, (2)'s waiver option can be applicable. Since this product is a parenteral solution intended solely for administration by injection, the following CFR can be applicable to the waiver:

CFR 320.22 "Criteria for waiver of evidence of in vivo bioavailability or bioequivalence."

(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration **as a drug product that is the subject of an approved full new drug application** or abbreviated new drug application.

The missing critical information for this NDA is the underlined portion of the last 2 lines above. Because there is no approved levothyroxine sodium injection product as reference, this waiver is not applicable. Thus, the sponsor needs to conduct a study to characterize the bioavailability of their levothyroxine sodium injection to satisfy the CFR 320.21.

The Sponsor's Submission

The sponsor cited the Maxon et al. article (see Question 2.6.1 below) to provide the relative bioavailability data between SYNTHROID intravenous injection and SYNTHROID oral tablet as well as LEVOTHROID oral tablet (*Int J Clin Pharmacol Ther Toxicol* 1983;21:379-82). The Maxon et al. article could have provided the sponsor's to-be-marketed levothyroxine sodium injection bioavailability data via linking it to the oral levothyroxine bioavailability data. However, the NDA approval dates for SYNTHROID and LEVOTHROID oral tablets are July 24, 2002 and October 24, 2002, respectively (Drugs@FDA). Thus, Maxon et al. studied unapproved SYNTHROID and LEVOTHROID oral tablets before August 21, 1983 (publication date). Had the sponsor studied any approved oral levothyroxine products, they may satisfy the waiver requirement via linking the bioavailability of levothyroxine sodium injection to the bioavailability of an approved oral levothyroxine product(s).

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.