CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202231Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**202231**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**August 30th 2010**
PRODUCT:	**Levothyroxine Sodium for Injection**
INTENDED CLINICAL POPULATION:	**Treatment for Myxedema Coma, (b) (4)**
SPONSOR:	**APP Pharmaceuticals, LLC**
DOCUMENTS REVIEWED:	**EDR**
REVIEW DIVISION:	**DMEP (HFD-510)**
PHARM/TOX REVIEWER:	**Miyun Tsai-Turton, PhD, MS**
PHARM/TOX SUPERVISOR:	**Karen Davis-Bruno, PhD**
DIVISION DIRECTOR:	**Mary Parks, MD**
PROJECT MANAGER:	**Linda Galgay**

Date of review submission to DARRTS: April 8th 2011

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

Pharam/tox recommends approval of this application.

B. Recommendation for nonclinical studies

No further animal studies will be needed.

C. Recommendations on labeling

See pharm/tox comments on labeling on pages 61-62.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

APP Pharmaceuticals, LLC did not conduct any animal studies with regards to pharmacology, pharmacokinetics, or toxicology studies in support of their Levothyroxine Sodium for Injection. The sponsor based their nonclinical data on published literature through Medline and Toxnet databases. Currently, there are no other injectable levothyroxine products currently approved by the FDA. Most studies found in literature have different routes of exposure rather than IV, which is the intended route of exposure.

As similar to other oral levothyroxine products, the animal toxicity of levothyroxine is mostly associated with expected exaggerated levothyroxine pharmacology (i.e. hyperthyroidism - decreased body weight or increased heart rate) at high doses. Because there was no toxicokinetic information available in the literature, it is difficult to correlate thyroid hormone toxicity with exposure or maximal levothyroxine concentration or relate to human exposure. On the other hand, since this IV levothyroxine is intended to use in hospitals for an acute rescue (i.e. (b) (4) myxedema coma) (b) (4) any IV levothyroxine-related adverse effects (i.e. hyperthyroidism) can be easily monitored or reversed. Also, due to severe hypothyroid states of these patients, the risk of having these hyperthyroidism-associated adverse effects would be small, even if it is at a much higher IV dose of levothyroxine when compared to oral levothyroxine which is used to maintain thyroid hormone homeostasis.

There were several impurities identified in the drug substance/product. Since they are all within acceptable limits, no animal study is needed to further characterize these impurities.

In summary, the sponsor is relying on published literature to support this IV levothyroxine product. Published literature seems to reveal a similar profile, regarding to pharmacokinetic (no apparent difference in AUC between an injectable and oral product) and toxicity (hyperthyroidism-associated adverse effects). In addition, the sponsor is relying on physicochemical characterization of identity as there is an absence of bridging animal toxicology data. Based on CMC review, both drug substance (referenced to DMF (b) (4) and drug products (e.g. impurities levels are within ICHQ3) are consistent with the monograph. Therefore, there is no safety nonclinical concern at this time.

B. Pharmacologic activity

Levothyroxine Sodium for Injection is a synthetic T_4, which is identical to that produced in the human thyroid gland. The function of thyroid hormone has been well-characterized in human.

C. Nonclinical safety issues relevant to clinical use

The sponsor did not have any bridging animal data with their IV levothyroxine product. Therefore, it is not possible to directly identify any potential nonclinical safety issue that is specifically related to this product.

Based on animal data from literature with levothyroxine and information from other approved oral levothyroxine products, there would be no safety issue except an exaggerated pharmacological effect of levothyroxine (i.e. hyperthyroidism) when it is overcompensated. Since this product will be used as hospital rescue therapy, overcompensation should not be problematic. This Levothyroxine Sodium for Injection by APP Pharmaceuticals will be the first injectable levothyroxine on the market.

It seems that both IV and oral levothyroxine have very similar profiles (i.e. no major differences in AUC and hyperthyroidism-related toxicity). However, with no bridging animal data on this IV levothyroxine product, similarity of products would be determined by physicochemical means by CMC. The CMC has communicated that the characterization of both drug substance and drug product are consistent with the monograph.

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