CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202231Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	June 2, 2011
From	Dragos Roman MD
Subject	Cross-Discipline Team Leader Review for an intravenous levothyroxine product
NDA/BLA # **Supplement#**	202-231 0
Applicant	APP Pharmaceuticals, LLC
Date of Submission	August 30, 2010
PDUFA Goal Date	June 30, 2010
Proprietary Name / Established (USAN) names	Levothyroxine Sodium for Injection/ Levothyroxine Sodium for Injection
Dosage forms / Strength	Three presentations containing the following strengths of levothyroxine sodium: 100 mcg/6.5 mL vial, 200 mcg/10 mL vial, 500 mcg/10 mL vial
Proposed Indication(s)	Treatment of myxedema coma
Recommended:	Approval

1. Introduction

Levothyroxine Sodium for Injection is a marketed unapproved drug used for the treatment of myxedema coma and other forms of hypothyroidism in which oral levothyroxine administration is not feasible. On December 18, 2006, APP Pharmaceuticals, the manufacturer of Levothyroxine Sodium for Injection (and sole manufacturer of an intravenous levothyroxine product at this time), was notified via a Warning Letter issued by the FDA Chicago District that, in order to lawfully market this product, it will need to submit a New Drug Application. A pre-IND meeting was held with the Agency on March 18, 2008, at which time APP Pharmaceuticals received advice from multiple review disciplines. Specifically, FDA requested that, given the diversity of information available in the medical literature, the company provide a clear justification for the proposed dosing regimen to be labeled for the treatment of myxedema; in addition, the Agency requested relative bioavailability data between oral and intravenous (IV) levothyroxine to guide dose conversion between these two regimens.

APP Pharmaceuticals submitted the current NDA (202-231) on August 30, 2010 under Section 505(b)(2) of the Food, Drug, and Cosmetics Act. The preclinical, clinical pharmacology, and clinical sections of the NDA contain exclusively data derived from published literature. From an approvability standpoint two issues are central to this submission: 1) the demonstration that the drug substance specifications (including identity, purity, excipient characterization) meet Agency standards, and 2) whether the literature published with intravenous levothyroxine in

myxedema coma is sufficient to identify a safe and effective treatment regimen, and if such information can be organized in a cohesive and informative label.

2. Background

Levothyroxine has a very long history of use in humans. Following the discovery of thyroxine in 1914, the elucidation of its chemical structure in 1926 and its subsequent synthesis, it has been used as replacement therapy for more than half a century. Intravenous formulations of levothyroxine have been introduced in the treatment of myxedema coma in the early 1960's.

The basic physiology of levothyroxine has been largely elucidated and is relatively well understood. This knowledge has its origins in an extensive body of medical literature spanning multiple decades of investigations and its therapeutic use is summarized in standard textbooks and professional society guidelines (e.g. Endocrine Society, American Thyroid Association). Although there are obvious differences between oral and IV levothyroxine products, mostly related to the route of administration, rate of absorption, and specific dosing, the clinical effect can be largely extrapolated from oral to intravenous products. No less importantly, the toxicity profile of levothyroxine in humans is well characterized on the basis of medical conditions of thyroid hormone excess or inappropriate use.

Myxedema coma is the most severe form of hypothyroidism. It is an exceedingly rare medical condition - an incidence rate of 0.22 per 1,000,000 per year has been reported - with an associated mortality as high as 80% if left untreated. There are only approximately 300 cases of myxedema coma reported to date in the medical literature.

At the time of NDA submission the applicant proposed the following indication:

> L-Thyroxine for Injection is indicated for treatment of myxedema coma, (b) (4)

The Division took the position tha (b) (4) The applicant agreed and, in an amendment dated May 13, 2001, stated that "that the only indication to be listed on the drug product labeling is myxedema coma".

3. CMC/Device

The drug substance for Levothyroxine Sodium for Injection is levothyroxine, identical in structure with the eponymous hormone. The drug product is a lyophilized powder containing levothyroxine sodium along with the following excipients: dibasic sodium phosphate heptahydrate, mannitol, and sodium hydroxide. It is packaged in amber glass vials (the drug product is photolabile) at three dosage strengths: 100 mcg/vial, 200 mcg/vial and 500 mcg/vial, and is stored at room temperature. These three dosage forms were selected with the goal of supporting a range of loading doses of 300-500 mcg and maintenance doses of 50 mcg and 100 mcg. Once reconstituted in 0.9% sodium chloride for injection, the product is to be used immediately (it is, in fact, stable for up to 4 hours at room temperature).

The drug substance specifications were found to be acceptable by the CMC reviewer and they met all the requirements of the current USP monograph, as did all the excipients. In addition, all impurities met compendial requirements as well. A shelf-life of (b) (4) was granted for storage at room temperature (b) (4) because of insufficient real-time stability data.

There are no CMC issues to prevent approvability. Both the primary CMC review (Dr. Leginus; DARRTS 4/29/2011) and secondary review (Dr. Al Hakim; DARRTS 4/29/2011) recommend approval of the application, and there are no requests or recommendations for postmarketing studies. The microbiology review also recommends approval, indicating that no deficiencies were identified regarding the sterility of the drug product. Finally, the CMC review also indicates that "acceptable cGMP recommendations have been received from the Office of Compliance for all manufacturing and testing facilities."

4. Nonclinical Pharmacology/Toxicology

The applicant did not conduct any pharmacology, pharmacokinetics, or toxicology animal studies with Levothyroxine Sodium for Injection. Instead, the nonclinical data presented in this application summarizes information from published literature, most of which was obtained with levothyroxine administered via routes other than IV. The reviewer comments that in the absence of toxicokinetic information it is difficult to predict human exposure and toxicity. On the other hand, the absence of a clear relationship between toxic animal doses and proposed human doses is counterbalanced by information provided by clinical experience in humans (which is quite extensive), by the fact that IV levothyroxine is administered to patients in a controlled hospital setting for a condition characterized by low or absent endogenous levothyroxine and, very importantly, by the mode of administration which involves titration to a desired pharmacodynamic and clinical response.

It is anticipated that the toxicity profile of intravenous levothyroxine in humans will be dictated by the exaggerated pharmacological effect of levothyroxine (i.e. symptoms of hyperthyroidism) and/or the impurity profile. While with respect to the former, appropriate

human dose selection and careful clinical monitoring should prevent such toxicity. Regarding the latter, the impurities identified in the drug product were all found to be within acceptable limits, and no animal studies were felt to be needed in order to further characterize them. In final analysis, the pharmacology/toxicology reviewer recommends approval of Levothyroxine Sodium for Injection for the treatment of myxedema coma.

In addition, one needs to acknowledge that the role of a preclinical toxicology program for a product whose active moiety is a small molecule identical structurally to an endogenous hormone, as is the case with levothyroxine (or other hormones for that matter), is different when compared to a chemical compound for which there is no human counterpart. Such difference exists not only because we understand better the physiological and pharmacological effects of a native product but, even more so, because of the availability of human "toxicology" data provided by pathological conditions of hormone excess, such as hyperthyroidism. In such cases the CMC confirmation of identity and purity is a considerable step in providing reassurance on the safety of the product.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review recommends approval of the application. As was the case with the preclinical pharmacology/toxicology section of the submission, the applicant did not conduct any clinical pharmacology studies, relying instead exclusively on published literature.

Analysis of the published information indicates that, once injected, levothyroxine distributes rapidly to target tissues and is indistinguishable from endogenous levothyroxine. It has a relatively long half-life (6 – 8 days for euthyroid patients and 9 – 10 days for myxedema patients) primarily due to the fact that > 99% of plasma levothyroxine is protein bound, which protects it from rapid degradation and excretion. Only unbound hormone is metabolically active. The major metabolic pathway of degradation is sequential deiodination that occurs in the thyroid, liver, kidneys, placenta and fibroblasts. Another route of degradation is hepatic glucuronidation and sulfation, followed by excretion into the bile and intestine from which it can be recirculated enterohepatically. The major route of excretion is renal, and only 20% is eliminated in the stool.

The pharmacodynamic response in myxedema coma is illustrated in Figure 4 of the clinical pharmacology review[1], which depicts the time course of TSH reduction following the administration of a levothyroxine dose (428 mcg) at the upper end of the proposed levothyroxine starting dose (300-500 mcg). A 32% reduction in TSH of is observed within 24 hours of IV levothyroxine administration; the TSH reduction continued during maintenance

[1] Reproduced from Ridgeway EC, McCammon JA, Benotti J, et al. Acute metabolic responses in myxedema to large doses of intravenous L-thyroxine. *Ann Intern Med* 1972;77:549-555.

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