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APPLICATION NUMBER:

210632Orig1s000

SUMMARY REVIEW

Cross Discipline Team Leader (CDTL) Memorandum

Date: March 19, 2019

From: Shannon Sullivan, M.D., PhD, Team Leader (Acting), Division of Metabolism and Endocrinology Products

Through: William Chong, M.D., Deputy Division Director (Acting), Division of Metabolism and Endocrinology Products

Subject: Recommendation for approval of NDA 210632 [Levothyroxine sodium for injection (100 mcg/5 mL, 200 mcg/5 mL, and 500 mcg/5 mL) Ready To Use (RTU) liquid formulation for treatment of myxedema coma]

Introduction:

Myxedema coma is a rare, yet serious clinical condition caused by severe hypothyroidism. Treatment of this condition consists of administration of thyroid hormone, typically via intravenous administration, along with other supportive care.

Levothyroxine sodium for injection is a form of synthetic thyroid hormone for intravenous (b) (4). FDA has previously approved a levothyroxine sodium for injection (NDA 202231) that is available as a lyophilized powder for reconstitution prior to injection.

On June 15, 2018, Fresenius Kabi USA, LLC (formerly known as APP Pharmaceuticals, LLC) submitted a New Drug Application (NDA) for levothyroxine sodium for injection 100 mcg/5 mL, 200 mcg/5 mL, and 500 mcg/5 mL Ready To Use (RTU) liquid formulations under section 505(b)(2) of the Federal Food, Drug, and Cosmetic (FD&C) Act for the treatment of myxedema coma.

This memorandum will discuss the basis for my recommendation to approve this NDA and the Applicant's proposal for addressing the Pediatric Research Equity Act (PREA).

Basis for Approval:

No clinical studies were conducted to support the current NDA. Instead, the applicant is proposing to rely upon the FDA's previous findings of safety and efficacy for the listed drug (LD), levothyroxine sodium for injection single dose vials (NDA 202231). Of note, the sponsor of this NDA is also the NDA holder of the LD (NDA 202231), which was approved in 2011 based on published literature.

The proposed product has the same active ingredient sourced from the same drug substance manufacturer as the LD (both NDAs reference the same Drug Master File). It differs from the LD in the excipients and in its presentation as a pre-diluted, RTU formulation.

The Applicant is proposing to rely upon Chemistry, Manufacturing, and Controls (CMC) data to support the bridge between the NDA product and the listed drug. Rather than conducting an in vivo assessment of bioavailability/bioequivalence to support reliance upon FDA's previous findings, the Applicant requested a waiver, citing 21 CFR 320.22(b)(1) and on the basis that the bioavailability/bioequivalence is self-evident, as both products are administered intravenously.

The biopharmaceutics reviewer from the Office of Pharmaceutical Quality (Sarah Ibrahim) reviewed the requested waiver and the basis for the waiver. Noting that the inactive ingredients are not the same for the proposed drug product and the LD, Dr. Ibrahim communicated that the requested waiver cannot be granted under 21 CFR 320.22 (b)(1). Referencing 21 CFR 320.24(b)(6), Dr. Ibrahim requested additional justification from the Applicant to support that the differences between the proposed drug product and the LD will not affect the pharmacokinetic (PK) profile, and that the pH and osmolality are similar between the two products.

The Applicant provided a response to this request on August 28, 2018. Dr. Ibrahim reviewed the provided data and concluded that differences between the two products would not affect the PK profile or clinical safety and efficacy. Based on this, she concluded that an in vivo bioequivalence bridging study is not needed, and that the waiver could be granted.

Subsequently, the CMC data supports reliance upon FDA's previous findings for NDA 202231.

As noted previously, the LD was approved based on published literature. As such, reliance upon FDA's previous findings for NDA 202231 is also considered to be reliance upon the same published literature (see Dr. Naomi Lowy's May 12, 2011, Clinical Review under NDA 202231). While additional published literature is cited by the applicant in the current NDA submission, it was not considered to be necessary to support the safety or effectiveness of the NDA product.

The rationale for approval of this 505(b)(2) application (i.e., the bridge between the proposed drug product and the LD) was reviewed by the 505(b)(2) Review Committee on March 18, 2019. The committee agreed that the NDA under review is sufficiently bridged to the published literature (as was the case for the LD [NDA 202231]) because the proposed product is an injectable solution with the same active moiety and the same indication as the LD. The 505(b)(2) Review Committee concluded that "there is no NEW reliance beyond what was originally relied upon for the applicant's powder for injection NDA 202231."

Pediatric Study Plan:

The Applicant submitted a proposed Pediatric Study Plan (PSP) to PIND 135637. In that PSP, the Applicant proposed to request a full waiver from pediatric studies, as studies in pediatric patients with myxedema coma are impossible or highly impracticable. The Applicant also noted in the PSP that a full waiver is consistent with that granted for the LD (NDA 202231). The Applicant's proposal was discussed with the Pediatric Review Committee on December 13, 2017, and an Agreed Initial PSP was issued with a plan for request of a full waiver.

In this NDA submission, the Applicant submitted the Agreed PSP requesting a full waiver. Pediatric studies of patients with myxedema coma remain impossible or highly impracticable. On February 27, 2019, the Pediatric Review Committee concurred with the plan for a full waiver in pediatric patients as presented in the Agreed Initial PSP. I also agree with the request for a full waiver.

CDTL Recommendation:

The bridge between the proposed drug product and the LD was established based on CMC data. While, in general, in vivo assessments are required to support a scientific bridge between two products, it is appropriate to waive this requirement for this product. As noted in the biopharmaceutics review, differences between the proposed drug product and the LD (i.e., differences in excipients, pH, osmolality) are unlikely to result in different PK characteristics or in differences in clinical safety or efficacy. The drug substance for both products is produced by the same manufacturer, and the product is intended solely for intravenous administration. I agree that the quality characteristics are sufficient to bridge between the proposed drug product and the LD, and that in vivo bioequivalence does not need to be demonstrated to allow reliance upon findings for safety and efficacy from NDA 202231.

While the Applicant also submitted literature references in support of the safety and effectiveness of the proposed product, much of the literature was previously submitted and reviewed to support approval of the LD. Additional literature citations published since the 2011 approval of NDA 202231 were submitted to support approval of the proposed product, none of which contain new safety or effectiveness data necessary for approval or that alter the risk/benefit profile of levothyroxine sodium injection for treatment of myxedema coma.

In conclusion, based on the above, I recommend approval of NDA 210632, levothyroxine sodium for injection RTU formulations for treatment of myxedema coma.

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/s/

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03/19/2019 03:36:55 PM

WILLIAM H CHONG
03/19/2019 04:20:51 PM
I agree with Dr. Sullivan's assessment and recommendation for approval. This memorandum also serves as the Divisional Memo.