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NOTICES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N-0314]

Prescription Drug Products; Levothyroxine Sodium

Thursday, August 14, 1997

*43535 AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that orally administered drug products containing levothyroxine sodium are new drugs. There is new information showing significant stability and potency problems with orally administered levothyroxine sodium products. Also, these products fail to maintain potency through the expiration date, and tablets of the same dosage strength from the same manufacturer vary from lot to lot in the amount of active ingredient present. This lack of stability and consistent potency has the potential to cause serious health consequences to the public. Manufacturers who wish to continue to market orally administered levothyroxine sodium products must submit new drug applications (NDA's); manufacturers who contend that a particular drug product is not subject to the new drug requirements of the Federal Food, Drug, and Cosmetic Act (the act) should submit a citizen petition. FDA has determined that orally administered levothyroxine sodium products are medically necessary, and accordingly the agency is allowing current manufacturers 3 years to obtain approved NDA's.

EFFECTIVE DATE: August 14, 1997.

DATES: A citizen petition claiming that a particular drug product is not subject to the new drug requirements of the act should be submitted no later than October 14, 1997.

After August 14, 2000, any orally administered drug product containing levothyroxine sodium, marketed on or before the date of this notice, that is introduced or delivered for introduction into interstate commerce without an approved application, unless found by FDA to be not subject to the new drug requirements of the act under a citizen petition submitted for that product, will

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be subject to regulatory action.

ADDRESSES: All communications in response to this notice should be identified with Docket No. 97N-0314 and directed to the appropriate office named below:

Applications under section 505 of the act (21 U.S.C. 355): Documents and Records Section (HFA-224), 5600 Fishers Lane, Rockville, MD 20857.

Citizen petitions (see §10.30 (21 CFR 10.30)) contending that a particular drug product is not subject to the new drug requirements of the act: Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

Requests for an opinion on the applicability of this notice to a specific product: Division of Prescription Drug Compliance and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT: Christine F. Rogers, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine (T sub4). Thyroid hormones affect protein, lipid, and carbohydrate metabolism; growth; and development. They stimulate the oxygen consumption of most cells of the body, resulting in increased energy expenditure and heat production, and possess a cardiostimulatory effect that may be the result of a direct action on the heart.

Levothyroxine sodium was first introduced into the market before 1962 without an approved NDA, apparently in the belief that it was not a new drug. Orally administered levothyroxine sodium is used as replacement therapy in conditions characterized by diminished or absent thyroid function such as cretinism, myxedema, nontoxic goiter, or hypothyroidism. The diminished or absent thyroid function may result from functional deficiency, primary atrophy, partial or complete absence of the thyroid gland, or the effects of surgery, radiation, or antithyroid agents. Levothyroxine sodium may also be used for replacement or supplemental therapy in patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

Hypothyroidism is a common condition. In the United States, 1 in every 4,000 to 5,000 babies is born hypothyroid. Hypothyroidism has a prevalence of 0.5 percent to 1.3 percent in adults. In people over 60, the prevalence of primary hypothyroidism *43536 increases to 2.7 percent in men and 7.1 percent in women.

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Because congenital hypothyroidism may result in irreversible mental retardation, which can be avoided with early diagnosis and treatment, newborn screening for this disorder is mandatory in North America, Europe, and Japan.

In addition to the treatment of hypothyroidism, levothyroxine sodium may be used to suppress the secretion of thyrotropin in the management of simple nonendemic goiter, chronic lymphocytic thyroiditis, and thyroid cancer. Levothyroxine sodium is also used with antithyroid agents in the treatment of thyrotoxicosis to prevent goitrogenesis and hypothyroidism.

II. Levothyroxine Sodium Products Must Be Consistent in Potency and Bioavailability

Thyroid replacement therapy usually is a chronic, lifetime endeavor. The dosage must be established for each patient individually. Generally, the initial dose is small. The amount is increased gradually until clinical evaluation and laboratory tests indicate that an optimal response has been achieved. The dose required to maintain this response is then continued. The age and general physical condition of the patient and the severity and duration of hypothyroid symptoms determine the initial dosage and the rate at which the dosage may be increased to the eventual maintenance level. It is particularly important to increase the dose very gradually in patients with myxedema or cardiovascular disease to prevent precipitation of angina, myocardial infarction, or stroke.

If a drug product of lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on one product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of greater potency or bioavailability could result in toxic manifestations of hyperthyroidism such as cardiac pain, palpitations, or cardiac arrhythmias. In patients with coronary heart disease, even a small increase in the dose of levothyroxine sodium may be hazardous.

Hyperthyroidism is a known risk factor for osteoporosis. Several studies suggest that subclinical hyperthyroidism in premenopausal women receiving levothyroxine sodium for replacement or suppressive therapy is associated with bone loss. To minimize the risk of osteoporosis, it is advisable that the dose be titrated to the lowest effective dose (Refs. 1 and 2).

Because of the risks associated with overtreatment or undertreatment with levothyroxine sodium, it is critical that patients have available to them products that are consistent in potency and bioavailability. Recent information concerning stability problems (discussed in section V of this document) shows that this goal is not currently being met.

III. Adverse Drug Experiences

Between 1987 and 1994, FDA received 58 adverse drug experience reports associated with the potency of orally administered levothyroxine sodium products. Forty-seven of the reports suggested that the products were subpotent, while nine suggested superpotency. Two of the reports concerned inconsistency in thyroid

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hormone blood levels. Four hospitalizations were included in the reports; two were attributed to product subpotency and two were attributed to product superpotency. More than half of the 58 reports were supported by thyroid function blood tests. Specific hypothyroid symptoms included: Severe depression, fatigue, weight gain, constipation, cold intolerance, edema, and difficulty concentrating. Specific hyperthyroid symptoms included: Atrial fibrillation, heart palpitations, and difficulty sleeping.

Some of the problems reported were the result of switching brands. However, other adverse events occurred when patients received a refill of a product on which they had previously been stable, indicating a lack of consistency in stability, potency, and bioavailability between different lots of tablets from the same manufacturer.

Because levothyroxine sodium products are prescription drugs marketed without approved NDA's, manufacturers are expressly required, under 21 CFR 310.305, to report adverse drug experiences that are unexpected and serious; they are not required, as are products with approved applications (see 21 CFR 314.80) periodically to report all adverse drug experiences, including expected or less serious events. Some adverse drug experiences related to inconsistencies in potency of orally administered levothyroxine sodium products may not be regarded as serious or unexpected and, as a result, may go unreported. Reports received by FDA, therefore, may not reflect the total number of adverse events associated with inconsistencies in product potency.

IV. Formulation Change

Because orally administered levothyroxine sodium products are marketed without approved applications, manufacturers have not sought FDA approval each time they reformulate their products. In 1982, for example, one manufacturer reformulated its levothyroxine sodium product by removing two inactive ingredients and changing the physical form of coloring agents (Ref. 6). The reformulated product increased significantly in potency. One study found that the reformulated product contained 100 percent of stated content compared to 78 percent before the reformulation (Ref. 7). Another study estimated that the levothyroxine content of the old formulation was approximately 70 percent of the stated value (Ref. 8).

This increase in product potency resulted in serious clinical problems. On January 17, 1984, a physician reported to FDA: "I have noticed a recent significant problem with the use of [this levothyroxine sodium product]. People who have been on it for years are suddenly becoming toxic on the same dose. Also, people starting on the medication become toxic on 0.1 mg [milligram] which is unheard of." On May 25, 1984, another physician reported that 15 to 20 percent of his patients using the product had become hyperthyroid although they had been completely controlled up until that time. Another doctor reported in May 1984 that three patients, previously well-controlled on the product, had developed thyroid toxicity. One of these patients experienced atrial fibrillation.

There is evidence that manufacturers continue to make formulation changes to orally administered levothyroxine sodium products. As discussed in section V of

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this document, one manufacturer is reformulating in order to make its product stable at room temperature. In a 1990 study (Ref. 5), one manufacturer's levothyroxine sodium tablets selected from different batches showed variations in chromatographs suggesting that different excipients had been used.

V. Stability Problems

FDA, in conjunction with the United States Pharmacopeial Convention, took the initiative in organizing a workshop in 1982 to set the standard for the use of a stability-indicating high-performance liquid chromatographic (HPLC) assay for the quality control of thyroid hormone drug products (Ref. 3). The former assay method was based on iodine content and was not stability-indicating. Using the HPLC method, there have been numerous reports indicating problems with the stability of orally administered levothyroxine sodium products in the past several years. Almost every manufacturer of *43537 orally administered levothyroxine sodium products, including the market leader, has reported recalls that were the result of potency or stability problems.

Since 1991, there have been no less than 10 firm-initiated recalls of levothyroxine sodium tablets involving 150 lots and more than 100 million tablets. In all but one case, the recalls were initiated because tablets were found to be subpotent or potency could not be assured through the expiration date. The remaining recall was initiated for a product that was found to be superpotent. During this period, FDA also issued two warning letters to manufacturers citing stability problems with orally administered levothyroxine sodium products.

At one firm, potency problems with levothyroxine sodium tablets resulted in destruction of products and repeated recalls. From 1990 to 1992, the firm destroyed 46 lots of levothyroxine sodium tablets that failed to meet potency or content uniformity specifications during finished product testing. In August 1989, this firm recalled 21 lots due to subpotency. In 1991, the firm recalled 26 lots in February and 15 lots in June because of subpotency.

An FDA inspection report concerning another manufacturer of levothyroxine sodium showed that 14 percent of all lots manufactured from 1991 through 1993 were rejected and destroyed for failure to meet the assay specifications of 103 to 110 percent established by the firm.

In March 1993, FDA sent a warning letter to a firm stating that its levothyroxine tablets were adulterated because the expiration date was not supported by adequate stability studies. Five lots of the firm's levothyroxine sodium tablets, labeled for storage within controlled room temperature range, had recently failed stability testing when stored at the higher end of the range. The warning letter also objected to the labeled storage conditions specifying a nonstandard storage range of 15 to 22 <<degrees>> C. FDA objected to this labeling because it did not conform to any storage conditions defined in United States Pharmacopeia (USP) XXII. In response, the firm changed the labeling instruction to store the product at 8 to 15 <<degrees>> C. The firm informed FDA that it would reformulate its levothyroxine sodium tablets to be stable at

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room temperature.

The five failing lots named in FDA's warning letter were recalled in April 1994. Previously, in December 1993, a lot of levothyroxine sodium tablets was recalled by the same firm because potency was not assured through the expiration date. In November 1994, the renamed successor firm recalled one lot of levothyroxine sodium tablets due to superpotency.

Another firm recalled six lots of levothyroxine sodium tablets in 1993 because they fell below potency, or would have fallen below potency, before the expiration date. The USP specifies a potency range for levothyroxine sodium from 90 percent to 110 percent. Analysis of the recalled tablets showed potencies ranging from 74.7 percent to 90.4 percent. Six months later, this firm recalled another lot of levothyroxine sodium tablets when it fell below labeled potency during routine stability testing. Content analysis found the potency of the failed lot to be 85.5 percent to 86.2 percent. Subsequently, an FDA inspection at the firm led to the issuance of a warning letter regarding the firm's levothyroxine sodium products. One of the deviations from good manufacturing practice regulations cited in that letter was failure to determine by appropriate stability testing the expiration date of some strengths of levothyroxine sodium. Another deviation concerned failure to establish adequate procedures for monitoring and control of temperature and humidity during the manufacturing process.

In April 1994, one manufacturer recalled seven lots of levothyroxine sodium products because potency could not be assured through the expiration date. In February 1995, the same manufacturer initiated a major recall of levothyroxine sodium affecting 60 lots and 50,436,000 tablets. The recall was initiated when the product was found to be below potency at 18-month stability testing.

In December 1995, a manufacturer recalled 22 lots of levothyroxine sodium products because potency could not be assured through the expiration date.

In addition to raising concerns about the consistent potency of orally administered levothyroxine sodium products, this pattern of stability problems suggests that the customary 2-year shelf life may not be appropriate for these products because they are prone to experience accelerated degradation in response to a variety of factors. Levothyroxine sodium is unstable in the presence of light, temperature, air, and humidity (Ref. 4). One study found that some excipients used with levothyroxine sodium act as catalysts to hasten its degradation (Ref. 5). In addition, the kinetics of levothyroxine sodium degradation is complex. Stability studies show that levothyroxine sodium exhibits a biphasic first order degradation profile, with an initial fast degradation rate followed by a slower rate (Ref. 4). The initial fast rate varies depending on temperature. To compensate for the initial accelerated degradation, some manufacturers use an overage of active ingredient in their formulation, which can lead to occasional instances of superpotency.

VI. References

The following references have been placed on display in the Dockets Management

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Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

(1) Paul, T. L. et al., "Long-term L-Thyroxine Therapy Is Associated with Decreased Hip Bone Density in Pre-menopausal Women," *Journal of the American Medical Association*, 259:3137-3141, 1988.

(2) Kung, A. W. C., and K. K. Pun, "Bone Mineral Density in Premenopausal Women Receiving Long-term Physiological Doses of Levothyroxine," *Journal of the American Medical Association*, 265:2688-2691, 1991.

(3) Garnick, R. I. et al., "Stability Indicating High-Pressure Liquid Chromatographic Method for Quality Control of Sodium Liothyronine and Sodium Levothyroxine in Tablet Formulations," in "Hormone Drugs," edited by J. L. Gueriguian, E. D. Bransome, and A. S. Outschoorn, United States Pharmacopeial Convention, pp. 504-516, Rockville, 1982.

(4) Won, C. M., "Kinetics of Degradation of Levothyroxine in Aqueous Solution and in Solid State," *Pharmaceutical Research*, 9:131-137, 1992.

(5) Das Gupta, V. et al., "Effect of Excipients on the Stability of Levothyroxine Sodium Tablets," *Journal of Clinical Pharmacy and Therapeutics*, 15:331-336, 1990.

(6) Hennessey, J. V., K. D. Burman, and L. Wartofsky, "The Equivalency of Two L-Thyroxine Preparations," *Annals of Internal Medicine*, 102:770-773, 1985.

(7) Stoffer, S. S., and W. E. Szpunar, "Potency of Levothyroxine Products," *Journal of the American Medical Association*, 251:635-636, 1984.

(8) Fish, L. H. et al., "Replacement Dose, Metabolism, and Bioavailability of Levothyroxine in the Treatment of Hypothyroidism; Role of Triiodothyronine in Pituitary Feedback in Humans," *The New England Journal of Medicine*, 316:764-770, 1987.*43538

VII. Legal Status

Levothyroxine sodium is used as replacement therapy when endogenous thyroid hormone production is deficient. The maintenance dosage must be determined on a patient-by-patient basis. Levothyroxine sodium products are marketed in multiple dosage strengths, that may vary by only 12 micrograms, thus permitting careful titration of dose. Because of levothyroxine sodium's narrow therapeutic index, it is particularly important that the amount of available active drug be consistent for a given tablet strength.

Variations in the amount of available active drug can affect both safety and effectiveness. Patients who receive superpotent tablets may experience angina, tachycardia, or arrhythmias. There is also evidence that overtreatment can cause osteoporosis. Subpotent tablets will not be effective in controlling hypothyroid symptoms or sequelae.

The drug substance levothyroxine sodium is unstable in the presence of light, temperature, air, and humidity. Unless the manufacturing process can be carefully and consistently controlled, orally administered levothyroxine sodium products may not be fully potent through the labeled expiration date, or be of consistent potency from lot to lot.

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There is evidence from recalls, adverse drug experience reports, and inspection reports that even when a physician consistently prescribes the same brand of orally administered levothyroxine sodium, patients may receive products of variable potency at a given dose. Such variations in product potency present actual safety and effectiveness concerns.

In conclusion, the active ingredient levothyroxine sodium is effective in treating hypothyroidism and is safe when carefully and consistently manufactured and stored, and prescribed in the correct amount to replace the deficiency of thyroid hormone in a particular patient. However, no currently marketed orally administered levothyroxine sodium product has been shown to demonstrate consistent potency and stability and, thus, no currently marketed orally administered levothyroxine sodium product is generally recognized as safe and effective. Accordingly, any orally administered drug product containing levothyroxine sodium is a new drug under section 201(p) of the act (21 U.S.C. 321(p)) and is subject to the requirements of section 505 of the act.

Manufacturers who wish to continue to market orally administered levothyroxine sodium products must submit applications as required by section 505 of the act and part 314 (21 CFR part 314). FDA is prepared to accept NDA's for these products, including section 505(b)(2) applications. An applicant making a submission under section 505(b)(2) of the act may rely upon investigations described in section 505(b)(1)(A) that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. For example, such an application may include literature supporting the safety and/or the effectiveness of levothyroxine sodium. A bioavailability study must be completed and submitted as part of an NDA, including a 505(b)(2) application, in order to evaluate the safety and efficacy of these products.

If the manufacturer of an orally administered drug product containing levothyroxine sodium contends that the drug product is not subject to the new drug requirements of the act, this claim should be submitted in the form of a citizen petition under §10.30 and should be filed to Docket No. 97N-0314 no later than October 14, 1997. Sixty days is the time allowed for such submissions in similar proceedings. (See §314.200(c) and (e).) Under § 10.30(e)(2), the agency will provide a response to each petitioner within 180 days of receipt of the petition. A citizen petition that contends that a particular drug product is not subject to the new drug requirements of the act should contain the quality and quantity of data and information set forth in § 314.200(e). Note especially that a contention that a drug product is generally recognized as safe and effective within the meaning of section 201(p) of the act is to be supported by the same quantity and quality of scientific evidence that is required to obtain approval of an application for the product. (See § 314.200(e)(1).)

Levothyroxine sodium products are medically necessary because they are used to treat hypothyroidism and no alternative drug is relied upon by the medical community as an adequate substitute. Accordingly, FDA will permit orally administered levothyroxine sodium products to be marketed without approved NDA's until August 14, 2000, in order to give manufacturers time to conduct the

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required studies and to prepare and submit applications, and to allow time for review of and action on these applications. This provision for continuation of marketing, which applies only to levothyroxine sodium products marketed on or before the publication of this notice, is consistent with the order in Hoffmann-La Roche, Inc. v. Weinberger, 425 F. Supp. 890 (D.D.C. 1975), reprinted in the Federal Register of September 22, 1975 (40 FR 43531) and March 2, 1976 (41 FR 9001).

After August 14, 2000 any orally administered drug product containing levothyroxine sodium, marketed on or before the date of this notice, that is introduced or delivered for introduction into interstate commerce without an approved application will be subject to regulatory action, unless there has been a finding by FDA, under a citizen petition submitted for that product as described above, that the product is not subject to the new drug requirements of the act.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505 (21 U.S.C. 352, 355)) and under authority delegated to the Deputy Commissioner for Policy (21 CFR 5.20).

Dated: August 7, 1997.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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