[Docket No. 76N–0052]

OVER-THE-COUNTER DRUGS

Decision On Theophylline As A Single Ingredient

The Food and Drug Administration (FDA) announces that, as a result of additional information, the Commissioner of Food and Drugs disagrees with the recommendation of the Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Panel ("the Panel") to allow theophylline to be made available over-the-counter (OTC) as a single ingredient. Any OTC drug product containing theophylline as a single ingredient is subject to immediate regulatory action.

In a notice published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38312), FDA proposed to establish conditions under which OTC cold, cough, allergy, bronchodilator, and antiasthmatic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Panel. The preamble to the proposal also included the complete conclusions and recommendations of the Panel.

The Panel's recommendations, and the proposed monograph, included its conclusion that several ingredients were safe and effective for OTC use that previously had been limited to prescription use or had been classified for OTC use at a dosage level lower than that recommended by the Panel. After reviewing those specific ingredients, the Commissioner made an initial determination not to disagree with the Panel's recommendations on the OTC use of a number of ingredients, including the use of theophylline as a single ingredient in OTC drug products. The Panel recommended that the adult daily dosage be 100 to 200 milligrams (mg) every 6 hours, not to exceed 800 mg in 24 hours.

The Commissioner stated, however, that although he did not challenge the judgment of the Panel regarding the safety of theophylline, he believed that there was a scientific issue as to whether the recommended dosage levels were therapeutically effective for a significant, identifiable population of asthmatics. Therefore, the Commissioner noted that theophylline was currently undergoing extensive review within the agency and, consequently, the Panel's recommendation might be subject to modification in the tentative final monograph.

Since publication of the Panel's recommendation, the Commissioner has received additional information that requires him to disagree at this time with the Panel's recommendation that theophylline be made available for use as a single ingredient in OTC drug products. This additional information, which was not available during the Panel's deliberations, indicates that the recommended therapeutic dose may be toxic to some individuals. This information suggests that the safe and effective use of this drug requires careful dosage titration based on theophylline serum concentrations.

In a recent report by Miles Weinberger, M.D. and Leslie Hendeles, Phar. D., "Pharmaco-therapy of Asthma," "The Journal of the Maine Medical Association," 67:9, 255–266, September 1976, the authors reported the relationship between theophylline dosage and the likelihood of achieving both therapeutic effect and toxicity. The report states that at the median effective dose (50th percentile) of 26 milligrams per kilogram per day (mg/kg/day) in 4 divided doses for children (or 1000 mg/day in 4 divided doses for adults), about 25 percent of the patient population is likely to be at risk of toxicity. The report shows that at the upper adult dosage recommended by the Panel, i.e., 800 mg/day, about 40 percent of the patient population will achieve a therapeutic effect; however, about 25 percent is likely to be at risk of toxicity. At the lower adult dosage recommended by the Panel, i.e., 400 mg/day, the report shows that none of the patient population is likely to be at risk of toxicity; however, only about 5 percent will achieve a therapeutic effect.

The report notes that current data suggest that theophylline is effective for suppressing chronic asthmatic symptoms when administered in dosages that achieve the therapeutic serum concentration range of 10 to 20 micrograms per milliliter (μg/ml). The Panel stated that studies indicate that variations between patients in their maintenance dose requirements are attributable to remarkable differences in the rate at which theophylline is metabolized. Because of variations in metabolism, about 20 percent of the adult patients receiving 800 mg/day will have theophylline serum concentrations of over 20 μg/ml and be at risk of toxicity. Drs. Weinberger and Hendeles recommend that, because serious toxicity such as seizures and death can occur from excessive serum concentrations (generally over 40 μg/ml) without earlier signs of lesser toxicity, clinical titration should be based on measurement of theophylline serum levels. A copy of this report has been placed on file in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857 and may be seen between the hours of 9 a.m. and 4 p.m., Monday through Friday.

Because of this additional information suggesting careful titration based on measurement of theophylline serum levels, the Commissioner concludes that, pending publication of the tentative final monograph, theophylline should not be made available as a single ingredient in OTC drug products. Therefore, he is stating his disagreement with the Panel's recommendation regarding the OTC use of theophylline as a single ingredient. This action will in effect limit the use of theophylline as a single ingredient to prescription drug products. This was the status of such use prior to publication of the Panel's recommendations. The Commissioner beleves that, because of the additional information, it is only prudent to maintain the existing status of the use of theophylline as a single ingredient; he also believes that allowing the use of theophylline to increase, pending publication of the tentative final monograph, is unwarranted.

The Commissioner advises that the use of theophylline, both as a single ingredient and in combination, and both in prescription and OTC drug products, is undergoing extensive review in FDA. Therefore, conditions under which theophylline is used may be subject to additional changes in the future. The Commissioner recommends that there not be any proliferation in the number of products containing theophylline, pending the announcement of the results of the review by FDA.

For the above reasons, the Commissioner does not at this time agree with the Panel's recommendation that theophylline be classified in Category I and be made available for OTC use as a single ingredient. Therefore, in accordance with § 330.13(b)(2) (21 CFR 330.13(b)(2)) setting forth the status of ingredients recommended for OTC use under the OTC drug review, published in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580), any product marketed containing theophylline as a single ingredient for OTC use is subject to immediate regulatory action.

Dated: December 3, 1976.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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