

Food and Drug Administration

Rockville, MD 20857

ADMINISTRATIVE STAFF

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JAN 28 1982

Kathryn V. Crean, Esq.
Assistant General Counsel
Burroughs-Wellcome Company
3030 Cornwallis Road
Research Triangle Park, NC 27709

Dear Ms. Crean:

This letter concerns the citizen petition dated March 16, 1981, that was submitted jointly by Dow Chemical Co., Burroughs-Wellcome Co., and Schering Corp., to support a change in the dosage schedule for pseudoephedrine for use as an oral nasal decongestant from 60 mg every 6 hours, not to exceed 240 mg in 24 hours, to 60 mg every 4 to 6 hours, not to exceed 240 mg in 24 hours. (A copy of this material is coded CP, Docket No. 76N-052N, and is on file in the Dockets Management Branch.)

The Bureau of Drugs has reviewed the data submitted in support of a dosage schedule of every 4 to 6 hours. The data include information on the pharmacokinetic behavior of pseudoephedrine and a review of adverse drug reactions related to pseudoephedrine. The submission contains a computer simulation of steady-state pseudoephedrine concentration profiles as a function of the dosage interval (i.e., every 4 hours vs. every 6 hours with a 240-mg maximum daily dose). The results show that the major determinant of the half-life of pseudoephedrine is urinary pH and that the half-life varies from 4 to 8 hours in normal individuals who are representative of the population at large. Based on the pharmacokinetic data, the Bureau concludes that 60 mg of pseudoephedrine given every 4 to 6 hours is permissible and more reflective of the achievable blood levels than a fixed dosage given every 6 hours.

In addition, eight studies were included in the petition. The Bureau notes that, the results of 6 of the studies are not relevant to the issue of whether the frequency of administration of pseudoephedrine is a factor in the incidence of side effects. However, two studies are supportive. The Kuntzman study demonstrates the influence of urine pH on the half-life of pseudoephedrine. When urinary pH is decreased, plasma half-life of pseudoephedrine is decreased markedly. In

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contrast, when urinary pH is increased, plasma half-life increases. The Brater study confirms Kuntzman's findings by demonstrating that both urine pH and urine flow are important determinants of the elimination of pseudoephedrine in humans. After reviewing the new information, the Bureau finds that there is sufficient evidence to show the efficacy of a total daily dose of 240 mg of pseudoephedrine and that it is reasonable to project similar plasma levels, whether this total daily dose is given as 60 mg every 4 to 6 hours or as 60 mg every 6 hours. Additionally, there is insufficient evidence in these data to show that an increase in adverse reactions occurs from administration of the drug at 4-hour intervals. The evidence relied upon in changing the Panel's original dosage interval recommendation from "every 4 hours" to "every 6 hours" did not directly relate the occurrence of any significant adverse drug reactions to the frequency of administration. That evidence was also based on plasma levels which may have been inaccurately or inadequately determined in view of the new data. Based on the new data, the Bureau, therefore, agrees that a more flexible dosage schedule for pseudoephedrine of 60 mg every 4 to 6 hours, not to exceed 240 mg daily, should be permitted.

The Bureau intends to recommend to the Commissioner that the dosage and directions in the tentative final monograph for use of pseudoephedrine as an oral nasal decongestant reflect this revision to allow an adult oral dosage of 60 mg every 4 to 6 hours not to exceed 240 mg in 24 hours. Likewise, the dosages for children will reflect the change in dosage interval.

We hope this information will be helpful.

Sincerely yours,



William E. Gilbertson, Pharm. D.
Director
Division of OTC Drug Evaluation
Bureau of Drugs

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