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Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

**Subject: Docket No. 81N-033P
Additional Data to be Considered Over-the-Counter Drug Products
for the Reduction or Prevention of Dental Plaque and Gingivitis:
Establishment of a Monograph (330.10)**

Dear Sir or Madam:

Colgate-Palmolive Company submits this additional data to be considered pursuant to 21 CFR 330.10 and requests that the Commissioner of Food and Drugs include zinc citrate as a Category I ingredient for safety and efficacy in the Final Monograph for Over-the-Counter Drug Products for the Reduction or Prevention of Dental Plaque and Gingivitis, Docket No. 81N-033P.

This submission includes the results of a six-month plaque and gingivitis study demonstrating the efficacy of zinc citrate in the reduction of plaque and gingivitis. This data in conjunction with 9 previously submitted clinical trials demonstrates the efficacy of zinc citrate and satisfying the requirements for its inclusion as a Category I ingredient for efficacy in the Final Monograph.

If you have any questions regarding this submission, please do not hesitate to contact me.

Respectfully,



Eugénie C. Acosta, RAC
Manager
Regulatory Affairs

81N-033P

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Additional Data to be Considered
Over-the-Counter Drug Products for the Reduction or Prevention of Dental Plaque
and Gingivitis: Establishment of a Monograph (330.10)
Docket No. 81N-033P

Introduction

Colgate-Palmolive Company submits this Additional Data to be Considered pursuant to 21 CFR 330.10 and requests that the Commissioner of Food and Drugs include zinc citrate as a Category I ingredient for safety and efficacy in the Final Monograph for Over-the-Counter Drug Products for the Reduction or Prevention of Dental Plaque and Gingivitis, Docket No. 81N-033P. This submission includes the results of a six-month plaque and gingivitis study demonstrating the efficacy of zinc citrate in the reduction of plaque and gingivitis. This demonstration of efficacy, in conjunction with previously submitted clinical studies, satisfies the requirements for the inclusion of zinc citrate as a Category I ingredient for efficacy in the Final Monograph.

Background

A request for data and information on all active ingredients used in OTC drug products bearing antiplaque and antiplaque related claims was issued September 19, 1990 (55 FR 38560). The Dental Plaque Subcommittee of the Dental Products Panel was formed to evaluate the submitted data and report their findings related to the safety and effectiveness of the ingredients for the reduction or prevention of dental plaque and gingivitis.

The subcommittee considered data submitted, published literature, and testimony through December 3, 1998 in arriving at recommendations for classification of the reviewed active ingredients. The recommendations appeared in a November 1998 panel report that classified the active ingredient zinc citrate as Category I for Safety and Category III for efficacy.

The panel recognized that zinc is ubiquitous in our environment and that the safety of zinc citrate has been extensively documented in recommending Category I for Safety. The panel found deficiencies in the data submitted in support of the efficacy of zinc citrate for plaque and gingivitis and recommended that zinc citrate be placed in Category III for Efficacy.

The efficacy data consisted of five short term clinicals, two six month trials and a three year trial. The deficiencies cited included limited background information on the studies, the basic design of the studies, and the clinical end points used in the studies. Based on the problems described in the studies the subcommittee concluded, "there are insufficient data available to permit final classification of the effectiveness of zinc citrate for use as an OTC antigingivitis, antiplaque agent". The panel made specific recommendations on what study information should be presented and how to present results in order to provide data to support efficacy for an OTC antigingivitis, antiplaque agent.

Additional Data

In response to these recommendations, Colgate-Palmolive Company submitted data of a well-controlled six-month study evaluating the efficacy of zinc citrate for controlling plaque and gingivitis (December 4, 2000). Ninety-nine (99) subjects completed this double-blind clinical study, where at both three and six month study examinations the zinc citrate dentifrice group exhibited statistically significant reductions in both plaque and gingivitis compared to the control group. At the six month study examination reductions met or exceeded 18% for both plaque and gingivitis. At this time Colgate-Palmolive Co. is submitting an additional protocol (Attachment 1) and results (Attachment 2) of a well-controlled six-month study which evaluates the efficacy of zinc citrate for controlling plaque and gingivitis.

The objective of this double blind clinical study, conducted in harmony with American Dental Association Guidelines, was to evaluate the efficacy of a dentifrice containing 2% zinc citrate and 0.76% sodium monofluorophosphate in a silica base for the control of supragingival plaque and gingivitis, compared to a control dentifrice containing 0.76% sodium monofluorophosphate in a silica base.

This study enrolled 111 subjects which were stratified into two treatment groups and balanced for baseline Quigley-Hein Plaque Index scores and baseline Loe-Silness Gingival Index scores. After qualification and study group assignment the subjects received a complete oral prophylaxis which included the removal of all supragingival plaque and calculus deposits. Subjects' teeth were then polished, and verification of plaque removal was done by the use of an erthyrosin dye. Subjects were instructed to brush their teeth for one minute twice daily (morning and evening) with their assigned dentifrice using a soft bristled toothbrush, and to refrain from any other hygiene procedures throughout the duration of the study. At three months and six months the same dental examiner evaluated the subjects for plaque and gingivitis. Supragingival plaque was scored according to the Turesky, et al. modification of the Quigley Hein Plaque index. Gingivitis was scored according to the Gingivitis Severity Index. This index measures the proportion of tooth surfaces in the mouth which have received high scores using the Mandel-Chilton modification of the Loe-Silness Gingival Index.

The results of this study show at both three and six month study examinations, a statistically significant reduction in supragingival plaque and gingivitis was observed for the group using the dentifrice containing 2.0% zinc citrate dentifrice compared to the group using the placebo dentifrice. At the three-month examination a statistically significant 13.1% reduction in supragingival plaque and statistically significant 58.6%

reduction in gingivitis was observed for the zinc citrate dentifrice group compared to the placebo dentifrice group. At the six-month examination a statistically significant 9.7% reduction in supragingival plaque and statistically significant 45.9% reduction in gingivitis was observed for the zinc citrate dentifrice group compared to the placebo dentifrice group.

Conclusion

Colgate Palmolive Company has provided the detailed protocol and results of a well-controlled clinical study demonstrating the clinical efficacy of zinc citrate in the reduction of supragingival plaque and gingivitis. This demonstration of efficacy, in conjunction with previously submitted data, justifies the classification of zinc citrate as a Category I active ingredient for efficacy as well as safety in the Final Monograph for Over-the-Counter Drug Products for the Reduction or Prevention of Dental Plaque and Gingivitis.