

ATTACHMENT 2

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September 19, 2002

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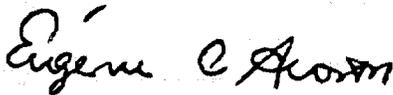
**Subject: Docket No. 81N-033P
Additional Data to be Considered Over-the-Counter Drug Products
for the Reduction or Prevention of Dental Plaque and Gingivitis:
Establishment of a Monograph (330.10)**

Dear Sir or Madam:

Colgate-Palmolive Company understands data submitted to the Agency on September 12, 2002, which supports 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 will be released to the public.

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

Respectfully,



Eugénie C. Acosta, RAC
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FACSIMILE COVER SHEET

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Date: September 19, 2002

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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)

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Dental Products Testing, Inc.

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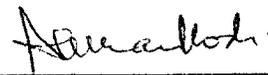
The Clinical Efficacy of
A Dentifrice Containing Zinc Citrate
in the Control of Plaque and Gingivitis

A Six-Month Clinical Study in Florida

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DATES OF STUDY: January 2001 – July 2001
DATE OF REPORT: August 2001

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ABSTRACT

The objective of this six-month, placebo-controlled, double-blind clinical study, conducted in harmony with American Dental Association guidelines, was to provide an assessment of the effectiveness of a dentifrice formulation containing 2.0% zinc citrate and 0.76% sodium monofluorophosphate in a silica base as compared to a placebo dentifrice containing 0.76% sodium monofluorophosphate in a silica base for the control of supragingival dental plaque and gingivitis.

Adult male and female subjects from Florida were entered into the study, and stratified into two treatment groups which were balanced for baseline Quigley-Hein Plaque Index scores and baseline Loe-Silness Gingival Index scores. Subjects received an oral prophylaxis and were instructed to brush their teeth twice daily (morning and evening) for one minute with their assigned dentifrice, using a soft-bristled toothbrush. Examinations for supragingival plaque and gingivitis were conducted after three months' and again after six months' participation in the study.

One hundred eleven (111) subjects complied with the protocol, and completed the entire six-month clinical study. At both the three- and six-month study examinations, the dentifrice group using the 2.0% zinc citrate dentifrice exhibited significantly less supragingival plaque and gingivitis (bleeding sites) than did the group using the placebo dentifrice.

Thus the results of this six-month clinical study support the conclusion that the dentifrice containing 2.0% zinc citrate and 0.76% sodium monofluorophosphate in a silica base provides a statistically significant, clinically-relevant level of efficacy for the control of supragingival plaque and gingivitis.

INTRODUCTION

The purpose of this six month, double-blind and independent clinical study was to evaluate the efficacy of a dentifrice formulation containing 2.0% zinc citrate and 0.76% sodium monofluorophosphate in a silica base for the control of supragingival dental plaque and gingivitis.

MATERIALS AND METHODS

This independent clinical study employed a double-blind, stratified, two treatment design. Adult male and female subjects from Florida were enrolled into the study based upon the following criteria:

- (i) subjects had to be between the ages of 18 and 70, in generally good health, and possess a minimum of 20 scorable teeth;
- (ii) subjects needed to be available for the duration of the study, and to sign an informed consent form;
- (iii) subjects were required to present, at baseline, a mean modified Quigley-Hein Plaque Index score of 1.5 or greater, and a mean modified Loe-Silness Gingival Index score of 1.0 or greater;
- (iv) subjects were excluded from the study if they had orthodontic appliances or removable prostheses, tumors of the soft or hard oral tissues, advanced periodontal disease, or if they had received antibiotic therapy during the two weeks prior to the start of the study.

Qualifying subjects were stratified into two balanced treatment groups according to their baseline Plaque and Gingival Index scores, age and sex.

The treatment groups were:

**A 2% Zinc
Citrate
Toothpaste**

A dentifrice formulation containing 2.0% zinc citrate and 0.76% sodium monofluorophosphate in a silica base (Colgate-Palmolive Company, New York, NY).

**Placebo
Toothpaste**

A dentifrice containing 0.76% sodium monofluorophosphate in a silica base (Colgate-Palmolive Company, New York, NY).

After qualification, and study group assignment, subjects were given a complete oral prophylaxis, which included the removal of all supragingival plaque and calculus deposits. The teeth were then polished, and complete plaque removal was verified by the use of an erythrosin dye. Subjects were provided with an initial supply of their assigned dentifrice along with an adult, soft-bristled toothbrush, and instructed to brush their teeth for one minute twice daily (morning and evening) in their customary manner using only the dentifrice and toothbrush provided, and to refrain from any other hygiene procedures throughout the duration of the study. The dentifrices were distributed in plain white tubes to ensure the double-blind nature of the study. Clinical study materials were re-supplied at regularly-scheduled intervals. When new tubes of dentifrice were issued, subjects returned their previous tube so that compliance with dentifrice use could be monitored.

Subjects returned to the clinical facility after three months and again after six months of product use, at which time they were evaluated by the same examiner for plaque and gingivitis. In addition, at each examination, the hard and soft tissues of the oral cavity of each subject were visibly inspected for the presence of adverse or unusual reactions.

CLINICAL SCORING PROCEDURE

Supragingival Dental Plaque

Supragingival plaque was scored according to the Turesky, *et al.* modification of the Quigley-Hein Plaque Index (1,2). Supragingival plaque on the facial and lingual surfaces of each tooth was disclosed, and scored according to the following criteria:

- | | | |
|---|---|--|
| 0 | = | No Plaque |
| 1 | = | Separate flecks of plaque at the cervical margin |
| 2 | = | A thin, continuous band of plaque (up to 1 mm) at the cervical margin |
| 3 | = | A band of plaque wider than 1 mm, but covering less than 1/3 of the side of the crown of the tooth |
| 4 | = | Plaque covering at least 1/3, but less than 2/3 of the side of the crown of the tooth |
| 5 | = | Plaque covering 2/3 or more of the side of the crown of the tooth |

Each tooth was scored in six areas: 1) mesio-facial; 2) mid-facial; 3) disto-facial; 4) mesio-lingual; 5) mid-lingual; and 6) disto-lingual. Third molars and those teeth with cervical restorations or prosthetic crowns were excluded from the scoring procedure. Whole-mouth mean scores were obtained by averaging the values recorded over all scorable tooth surfaces in the mouth.

Gingivitis

Gingivitis was scored according to the Gingivitis Severity Index(3) which measures the proportion of the tooth surfaces in the mouth which have received high scores using the Mandel-Chilton modification of the Loe-Silness Gingival Index (4,5). Specifically, the Gingivitis Severity Index indicates the proportion of scored tooth surfaces in the mouth whose assigned modified Loe-Silness Gingival Index scores were 2 or 3 (*i.e.*, bleeding sites).

The facial and lingual surfaces of each tooth were scored as follows:

- 0 = Absence of inflammation
- 1 = Mild inflammation: slight change in color and little change in texture
- 2 = Moderate inflammation: moderate glazing, redness, edema, hypertrophy. Tendency to bleed upon probing
- 3 = Severe inflammation: marked redness and hypertrophy. Tendency to spontaneous bleeding

Each tooth was scored in six areas: 1) mesio-facial; 2) mid-facial; 3) disto-facial; 4) mesio-lingual; 5) mid-lingual; and 6) disto-lingual. Third molars and those teeth with cervical restorations or prosthetic crowns were excluded from the scoring procedure. Whole mouth scores were obtained by dividing the total number of scorable tooth surfaces receiving a Quigley-Hein Index score of 2 and 3 by the total number of scorable tooth surfaces in the mouth.

STATISTICAL METHODS

An analysis of variance (ANOVA) was employed to compare the mean Plaque Index and Gingivitis Index scores obtained for the two test products groups at the baseline examination. Baseline-adjusted means were compared via analysis of covariance (ANCOVA) for the corresponding three- and six-month data. All statistical tests of hypotheses were two-sided, and employed a level of significance of $\alpha = 0.05$.

RESULTS

One hundred eleven (111) subjects completed the entire six months. A summary of the age and sex of the study population is presented in Table 1. The treatment groups were well-balanced with respect to these characteristics.

Throughout the study, there were no adverse effects on the oral hard or soft tissues which were observed by the dental examiner, or reported by the subjects when questioned concerning adverse effects.

Baseline Data

Table 2 presents a summary of the clinical data measured at the baseline examination for those subjects who went on to complete the entire six-month study. No statistically significant differences were indicated among the two treatment groups with respect to baseline scores among subjects who completed the study.

Three-Month Data

Table 3 presents a summary of the clinical data measured after three months' participation in the study.

The mean Plaque Index score for the zinc citrate dentifrice group was 2.144, while the mean Plaque Index score for the placebo dentifrice group was 2.467, yielding a statistically significant 13.1% reduction in supragingival plaque for the zinc citrate dentifrice group.

The mean Gingivitis Severity Index score for the zinc citrate dentifrice group was 0.048, while the mean Gingivitis Severity Index score for the placebo dentifrice group was 0.116, yielding a statistically significant 58.6% gingivitis (bleeding sites) reduction for the zinc citrate dentifrice group.

Six-Month Data

Table 4 presents a summary of the clinical data measured after six months' participation in the study.

The mean Plaque Index score for the zinc citrate dentifrice group was 2.041, while the mean Plaque Index score for the placebo dentifrice group was 2.259, yielding a statistically significant 9.7% reduction in supragingival plaque for the zinc citrate dentifrice group.

The mean Gingivitis Severity Index score for the zinc citrate dentifrice group was 0.053, while the mean Gingivitis Severity Index score for the placebo dentifrice group was 0.098, yielding a statistically significant 45.9% gingivitis reduction for the zinc citrate dentifrice group.

SUMMARY AND CONCLUSION

At both the three and six month study examinations, the group using the dentifrice containing 2.0% zinc citrate exhibited statistically significant reductions in both supragingival plaque and gingivitis compared to the placebo dentifrice group.

The results of this six-month clinical study support the conclusion that a dentifrice containing 2.0% zinc citrate and 0.76% sodium monofluorophosphate in a silica base provides a statistically significant and clinically meaningful level of efficacy for the control of supragingival plaque, and for the control of gingivitis, as compared to a placebo dentifrice containing 0.76% sodium monofluorophosphate in a silica base.

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TABLE 1

Summary of Age and Sex Characteristics for Subjects Who Completed the Six-Month Study

Dentifrice Group	Male	Female	Total	Mean Age
Placebo	22	34	56	38.6
Zinc Citrate	23	32	55	38.9

TABLE 2

**BASELINE CLINICAL DATA* FOR SUBJECTS
WHO COMPLETED THE SIX-MONTH STUDY**

INDEX	PLACEBO DENTIFRICE (N = 36)	ZINC CITRATE DENTIFRICE (N = 55)	STATISTICAL SIGNIFICANCE+
Plaque	2.579 ± 0.438	2.599 ± 0.393	NS
Gingivitis	0.145 ± 0.131	0.148 ± 0.116	NS

* Mean ± standard deviation

+ Significance of ANOVA comparison of baseline means. NS = non significant

TABLE 3

**RESULTS* AT THE THREE-MONTH EXAMINATION FOR
SUBJECTS WHO COMPLETED THE SIX-MONTH STUDY**

Index	Placebo Dentifrice (N = 56)	Zinc Citrate Dentifrice (N = 55)	Percent Reduction (vs. Placebo)	Statistical Significance+
Plaque	2.467 ± 0.424	2.144 ± 0.480	- 13.1	p < 0.05
Gingivitis	0.116 ± 0.084	0.048 ± 0.052	- 58.6	p < 0.05

* Mean ± standard deviation

+ Significance of ANCOVA comparison of baseline adjusted means

TABLE 4

**RESULTS* AT THE SIX-MONTH EXAMINATION FOR
SUBJECTS WHO COMPLETED THE SIX-MONTH STUDY**

Index	Placebo Dentifrice (N = 56)	Zinc Citrate Dentifrice (N = 55)	Percent Reduction (vs. Placebo)	Statistical Significance ⁺
Plaque	2.259 ± 0.470	2.041 ± 0.460	- 9.7	p < 0.05
Gingivitis	0.098 ± 0.112	0.053 ± 0.056	- 45.9	p < 0.05

* Mean ± standard deviation

+ Significance of ANCOVA comparison of baseline adjusted means

