

PROTOCOL# CRO-01/01-ZINC/PLAGIN-MP

**EFFICACY OF A DENTIFRICE
CONTAINING**

**2.0 % ZINC CITRATE
AND
0.76% SODIUM MONOFLUOROPHOSPHATE
IN A SILICA BASE**

IN THE CONTROL OF PLAQUE AND GINGIVITIS:

A SIX MONTH CLINICAL STUDY

SPONSOR:

**CLINICAL DENTAL RESEARCH
COLGATE PALMOLIVE TECHNOLOGY CENTER
COLGATE-PALMOLIVE COMPANY
909 RIVER ROAD
PISCATAWAY, NJ 08854**

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REVISIONS AND AMENDMENTS

JANUARY 17, 2001

1. The study will be conducted at Dental Products Testing, Inc.
by Dr. Suru Mankodi at 1497 Forest Hills Boulevard Suite G,
West Palm Beach, Florida 33406
2. Appendix III, Initial Screening Form-
This form is only one page so the line stating "page 1 of 2" is
incorrect. Please disregard.
3. Final Visit Form-
This form is incorrectly identified on page 5 as Appendix VII.
It is actually Appendix VIII.
4. A E Form-
This form is incorrectly identified on page 8 as Appendix VIII. It is
actually Appendix IX.
5. Study Supplies-
Placebo will be supplied in tubes (identical to test product) not plastic
bottles.
6. Subject Record Forms-
The Informed Consent Form will be completed by the subject and
reviewed by the Principal Investigator or his designate for accuracy
and completeness.

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OBJECTIVE

The objective of this study is to confirm the efficacy of a dentifrice formulation containing 2.0% Zinc Citrate, 0.76% Sodium Monofluorophosphate in a silica base as compared to a placebo dentifrice containing 0.76% Sodium Monofluorophosphate in a silica base in the control of plaque and gingivitis after an oral prophylaxis.

II. STUDY POPULATION

One hundred twenty subjects (120), ages 18-70 years will be entered into the study.

Inclusion Characteristics

1. Male and female subjects, ages 18-70, inclusive.
2. Availability for the six-month duration of the study.
3. Good general health.
4. Minimum of 20 uncrowned permanent natural teeth (excluding third molars).
5. Initial gingivitis index of at least 1.0 as determined by the use of the Loe and Silness Gingival Index.
6. Initial plaque index of at least 1.5 as determined by the use of the Quigley and Hein Plaque Index (Turesky Modification).
7. Signed Informed Consent Form.

Exclusion Characteristics

1. Presence of orthodontic bands.
2. Presence of partial removable dentures.
3. Tumor(s) of the soft or hard tissues of the oral cavity.
4. Advanced periodontal disease (purulent exudate, tooth mobility, and/or extensive loss of periodontal attachment or alveolar bone).
5. Five or more carious lesions requiring immediate restorative treatment.
6. Use of antibiotics any time during the one month prior to entry into the study.
7. Participation in any other clinical study or test panel within the one month prior to entry into the study.
8. Pregnant women or women who are breast feeding.
9. History of allergic reactions to dentifrice ingredients.

III. STUDY DESIGN

1. Configuration

This study will be a double-blind, stratified, two treatment, parallel clinical study. Groups will be randomly assigned to one of the two test dentifrices.

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2. Duration

All subjects will use their assigned dentifrice for six months. All subjects will discontinue product use at six months.

IV. DENTIFRICES

1. Dentifrice formulation containing 2.0 % zinc citrate, 0.76% sodium monofluorophosphate in a silica base. PIM#233273
2. Placebo Dentifrice containing 0.76% sodium monofluorophosphate in a silica base. PIM#233249

The dentifrice will be packaged in identical white tubes so as to ensure that neither the examiner nor the subjects are aware of the identity of the product. Formulations are shown in Appendix I.

V. PROCEDURE

1. Screening and Selection of Subjects

Candidates will report to the clinical facility having refrained from any oral hygiene procedures for 8 hours prior to their examination and having refrained from eating, drinking or smoking for four hours prior to their examination. They will sign an Informed Consent Form (Appendix II) and be screened by the examining dentist to identify those subjects who meet the inclusion/exclusion characteristics. The findings of this initial screening procedure will be recorded on the Initial Screening Form (Appendix III). Subjects who meet the inclusion/exclusion criteria characteristics will be entered into the study.

2. Oral Soft Tissue Examination

The initial screening procedure will include an oral soft tissue assessment to determine the eligibility of each subject to enter the study. All subjects will receive an evaluation of their oral soft tissues by the examining dentist. This evaluation will include an assessment of the soft palate, hard palate, gingival mucosa, buccal mucosa, mucogingival fold areas, tongue, sublingual and submandibular areas, salivary glands and the tonsillar and pharyngeal areas. The results from this evaluation will be recorded on the Oral Soft Tissue Assessment Form (Appendix IV).

3. Baseline Gingivitis Examination

The initial screening procedure will include a qualifying gingivitis examination to determine the eligibility of each subject to enter the study. The scoring procedure to be used to evaluate gingivitis will be the Loe and Silness Gingival Index.

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The examining dentist will dictate the findings of this examination to a trained recorder who will record the data onto the Gingivitis Examination Form (Appendix V).

4. Baseline Plaque Examination

The initial screening procedure will include a plaque examination to determine the eligibility of each subject to enter the study. The scoring procedure to be used to evaluate plaque will be the Quigley and Hein Plaque Index (Turesky Modification).

The examining dentist will dictate the findings of this examination to a trained recorder who will record the data onto the Plaque Examination Form (Appendix VI).

5. Stratification and Randomization of Subjects

Those subjects who satisfy the inclusion/exclusion criteria and sign an Informed Consent Form will be stratified by baseline gingivitis and plaque scores into two balanced groups.

Each group will then be randomly assigned to one of the two dentifrices.

6. Oral Prophylaxis

All subjects who meet inclusion/exclusion criteria will receive a complete oral prophylaxis after baseline gingivitis and plaque examinations. The prophylaxis procedure will be verified for its thoroughness by the use of a red disclosing solution.

7. Dentifrice Use at Home

Subjects will be provided with their assigned dentifrice and a soft-bristled adult toothbrush for home use. Subjects will be instructed to brush their teeth twice daily (in the morning and evening) for one minute.

8. Instructions to Subjects

Subjects will be instructed to use only the study dentifrice and toothbrush provided to them during the six-month study period. The test dentifrice and toothbrush will be resupplied at the Three Month Examination. Subjects will return to the clinical site with their used dentifrice and toothbrush before receiving new products.

Subjects will be instructed to refrain from using any other oral hygiene products such as other dentifrices or toothbrushes, mouthrinses, dental flosses, and interdental stimulators while they are participating in the study. There will be no restrictions regarding diet and smoking habits during the course of the study.

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9. Three Month Oral Soft Tissue Assessment

After three months' use of the test dentifrices, all subjects will receive an evaluation of their oral soft tissues. The same procedures used at the baseline oral soft tissue assessment will be repeated and the results will be recorded on the Oral Soft Tissue Assessment Form. (Appendix IV)

10. Three Month Gingivitis and Plaque Examinations

After three months' use of the test dentifrice, all subjects will report to the clinical facility, having refrained from oral hygiene procedures for eight hours before the visit and having refrained from eating, drinking, or smoking for four hours prior to the visit, to be evaluated by the examining dentist for gingivitis and plaque.

The same scoring procedures used at the baseline gingivitis and plaque examinations will be followed. A Gingivitis Examination Form and a Plaque Examination Form will be used to record data from these examinations. (Appendix V & VI)

A Visit Form will be completed for each subject at the Three Month Exam (Appendix VII).

11. Six Month Oral Soft Tissue Assessment

After six months' use of the test dentifrices, all subjects will receive an evaluation of their oral soft tissues. The same procedures used at the baseline oral soft tissue assessment will be repeated and the results will be recorded on the Oral Soft Tissue Assessment Form. (Appendix IV)

12. Six Month Gingivitis and Plaque Examinations

After six months' use of the test dentifrice, all subjects will report to the clinical facility, having refrained from oral hygiene procedures for eight hours before the visit and having refrained from eating, drinking, or smoking for four hours prior to the visit, to be evaluated by the examining dentist for gingivitis and plaque.

The same scoring procedures used at the baseline gingivitis and plaque examinations will be followed.

A Gingivitis Examination Form and a Plaque Examination Form will be used to record data from these examinations. (Appendix V & VI)

A Final Visit Form will be completed for each subject at the Six Month Exam (Appendix VII).

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VI. DENTAL TREATMENT DURING STUDY

Subjects will be instructed to refrain from routine dental treatment (except emergency) during the course of the study. Subjects who receive dental treatment, use antibiotics and women who become pregnant or breast feed must report these occurrences to the examining dentist.

VII. STATISTICAL ANALYSIS

Mean gingivitis and plaque scores will be computed for each subject using the data obtained from the baseline, three-month, and six-month examinations.

Mean within subject gingivitis and plaque scores will be computed as follows:

Total gingivitis scores for all scoring sites
divided by
Total number of scoring sites

Total plaque scores for all scoring sites
divided by
Total number of scoring sites

In addition, mean treatment group scoring site gingivitis and plaque scores will be computed by dividing the sum of the mean within subject scoring site and gingivitis and plaque scores by the total number of subjects in each group.

The three and six month plaque and gingivitis scores for the subjects in each dentifrice group will be compared using an Analysis of Variance. Statistical significance is declared if the p-value of the two-sided t-test 0.05 or less.

VIII. MONITORING OF STUDY

This study will be monitored by a staff member of Colgate's Clinical Dental Research Department at periodic intervals during the course of the study in order to ensure that the study is being conducted according to Good Clinical Practices Guidelines.

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IX. STUDY DISCONTINUATION PROCEDURES

A genuine effort will be made to determine the reason(s) why a subject fails to return for the necessary visit(s) and is dropped from the study.

Subjects could be dropped from the study if any of the following occurs:

1. Subject fails to report for a scheduled plaque and gingivitis examination.
2. Subject is treated with antibiotics during the course of the study.
3. Subject receives emergency dental treatment or medical treatment which might interfere with the parameters of the study.
4. Subject fails to substantially comply with the protocol requirements.
5. Subject develops an adverse reaction (Appendix VIII)
6. Sponsor elects to terminate the study.
7. Subject elects to terminate participation in the study.
8. Subject becomes pregnant or breast feeds.

The procedure to be followed by the study investigator if the sponsor terminates the study:

1. Notify the subject and complete Final Visit Form.
2. Notify the Institutional Review Board.
3. Return all materials provided by the sponsor.

X. SUBJECT RECORD FORMS

The following subject record forms will be completed by the Study Investigator according to the following schedule:

BASELINE VISIT

- o Informed Consent Form
- o Initial Screening Form
- o Baseline Oral Soft Tissue Assessment Form
- o Baseline Gingivitis Examination Form
- o Baseline Plaque Examination Form

THREE MONTH VISIT

- o Three Month Oral Soft Tissue Assessment Form
- o Three Month Gingivitis Examination Form
- o Three Month Plaque Examination Form
- o Three Month Visit form

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SIX MONTH VISIT

- o Six Month Oral Soft Tissue Assessment Form
- o Six Month Gingivitis Examination Form
- o Six Month Plaque Examination Form
- o Final Visit Form

XI. RESPONSIBILITIES OF INVESTIGATOR

The study investigator will have the responsibilities of ensuring that the protocol is adhered to, completing the required forms, advising the sponsor of any serious reaction and returning any unused products to the sponsor.

XII. STUDY SUPPLIES (15% SURPLUS)

- 650 4.8 oz. tubes of 2% Zinc Citrate Dentifrice
- 650 4.8 oz. plastic bottles of Placebo Dentifrice
- 800 Colgate Total Professional Soft-bristled adult toothbrushes.

XIII. STUDY SITE AND INVESTIGATOR

This study will be conducted at Dental Products Testing under the direction of Dr. Suru Mankodi.

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APPENDIX II INFORMED CONSENT FORM PAGE ONE OF THREE

Purpose

You are being considered for participation in a six (6) month clinical study to assess the effects of two (2) toothpastes on dental plaque and gum inflammation (gingivitis).

Benefits

Participation in this study may not benefit you personally. The results of the study may help assure that the dentifrice is safe for marketing to the general public.

Test Description

Approximately one hundred twenty (120) subjects will be utilized in this study. In order to be selected, you must meet certain criteria:

You must be in good general health.

You must be at least eighteen (18) years old and no older than seventy (70) years of age.

You must be available for the six (6) month duration of the study.

If you are a woman, you must not be pregnant or breast feeding.

The examining dentist must find that the condition of your teeth and gums are satisfactory for entry into the study.

You must have sufficient plaque and gingival inflammation as determined by an initial plaque and gingivitis examination by the examining dentist.

You must not have used any antibiotic during the one month prior to entry into the study.

You must not currently be participating or during the past month have participated in any other research study.

You must not be allergic to toothpaste ingredients.

At the start of the study you will report to the clinical facility without having brushed your teeth for eight hours for eight hours prior to your scheduled visit and without having used any other oral hygiene procedure. Also you should not eat, drink or smoke for 4 hours prior to your scheduled visit. Your teeth and gums will be examined by a dentist. If the examining dentist finds the condition of your teeth and gums satisfactory, you will be entered into the study (six-month duration). Your teeth will be cleaned by a dental hygienist or dentist which may cause bleeding or soreness temporarily. You will be assigned to use one of two (2) test toothpastes.

Subject's Initials

Date

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You will be given your assigned toothpaste and a soft adult toothbrush to use at home. You will be required to brush your teeth with the toothpaste and the toothbrush provided to you twice daily (mornings and evenings) for one (1) minute .

You will report back to the clinical facility for a plaque, gingivitis and oral soft tissue examination at three and six months. At each of these examination visits, you should return your supply of toothpaste and your toothbrush. At the three month examination visit you will be given a new supply of toothpaste and a new toothbrush for the remainder of the study duration.

In order to make the plaque on your teeth visible, you will be asked to rinse your mouth with red colored dye which has been approved for use as a food additive.

You must only use the dentifrice and toothbrush provided. These products should not be shared with any other member of your household.

You must not use any other oral hygiene products such as other toothpastes or toothbrushes, mouthrinses, dental floss, irrigation devices, etc. during the six (6) month study period. You are asked to refrain from routine dental treatment but should not defer any necessary or emergency dental treatment.

You are requested to inform the examining dentist immediately if you receive emergency dental treatment, take any antibiotic medication or receive dental treatment that interferes with this study, or if you become pregnant or breast feed.

Potential Risk

One of the toothpastes contains an ingredient called zinc citrate, which is found in commercially available toothpastes. No adverse side effects from the use of these toothpastes are anticipated in this study.

If you experience any problems or any research related injury, you are to contact Dr. Mankodi immediately at 1-561-434-3437. You understand that if any physical injury results from your use of the test products, the sponsoring company will be responsible for medical costs provided you seek medical attention as directed by the sponsoring company or as directed by the Study Investigator.

Subject's Initials

Date

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**APPENDIX II
INFORMED CONSENT FORM
PAGE THREE OF THREE**

Compensation

You will be monetarily compensated after you complete the study. If you do not complete the study of your own free will you may receive a pro-rated portion of the compensation at the discretion of the sponsor.

Right to Leave the Study

Your signature below signifies that you understand and agree to the above, and affirms that you have volunteered to participate of your own free will. Further, you assert that you are eighteen (18) years of age but not older than seventy (70) years of age and not nursing a baby or pregnant and that you were given the opportunity to ask questions about the study.

You may withdraw from this study at any time without prejudice. This study is conducted under the direction of Dr. Mankodi for the sponsoring company.

Any pertinent questions about this research or your rights concerning participation in this study will be answered by calling Dr. Mankodi at Dental Products Testing, 1-561-434-3437.

Confidentiality of Records

The records of your participation in this study are confidential and these records are available only to the Investigator, the sponsoring company and possibly the Food and Drug Administration of the United States. The results of this study may be published in a scientific journal and your initials and age, but not your name, may be used. You agree to verify, by letter, that you participated in this study, if called upon to do so.

Authorization

I have read and understand the nature, duration and purpose of this study and if selected, hereby voluntarily consent to participate.

I understand that a copy of this Informed Consent Form will be given to me.

I have had the opportunity to ask questions concerning all aspects of the study.

I understand that I may withdraw from the study at any time for any reason without prejudice.

Witness Signature

Subject Signature

Witness Name (PRINTED) Date

Subject Name (PRINTED) Date

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APPENDIX III

INITIAL SCREENING FORM

PAGE 1 of 2

SUBJECT NAME _____ DATE _____
SUBJECT NUMBER _____ SEX ____ AGE _____

1. Is subject at least 18 and less than 71 years of age? YES ___ NO ___
2. Is subject available for the six-month duration of the study? YES ___ NO ___
3. Is subject in good health? YES ___ NO ___
4. Does subject have 20 or more uncrowned permanent natural teeth (excluding third molars)? YES ___ NO ___
5. Does subject have a qualifying gingivitis index of at least 1.0 as determined by the Loe-Silness Gingival Index? YES ___ NO ___
6. Does subject have a qualifying plaque index of at least 1.5 as determined by the Quigley and Hein Plaque Index (Turesky Modification)? YES ___ NO ___
7. Has subject signed an Informed Consent Form? YES ___ NO ___

If answer to any of questions 1-7 is No, subject is ineligible for study. Subject should be dismissed and question 16 below completed. If subject is eligible, continue to questions 8-15.

8. Does subject have an orthodontic appliance ? YES ___ NO ___
9. Does subject use a removable partial denture? YES ___ NO ___
10. Does subject have a soft or hard tissue tumor of the oral cavity? YES ___ NO ___
11. Does subject have advanced periodontal disease (purulent exudate, tooth mobility, and/or extensive alveolar bone loss)? YES ___ NO ___
12. Does subject have five or more carious lesions requiring immediate restorative treatment? YES ___ NO ___
13. Has subject been on antibiotic therapy within the last month? YES ___ NO ___
14. Is subject pregnant or breast feeding? YES ___ NO ___
15. Is subject participating in any other clinical study now or has subject participated in a clinical study within the past month ? YES ___ NO ___

If answer to any of questions 8-15 is YES, subject is ineligible for study. Subject should be dismissed and Question 16 completed.

16. IS SUBJECT ELIGIBLE FOR ENTRY INTO THE STUDY? YES ___ NO ___

DATE

SIGNATURE, EXAMINING DENTIST

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APPENDIX IV
ORAL SOFT TISSUE EXAMINATION FORM

DATE _____ SUBJECT NAME _____ SUBJECT# _____

BASELINE _____ THREE-MONTH _____ SIX-MONTH _____

AREA	NORMAL
1. SOFT PALATE	YES _____ NO _____
2. HARD PALATE	YES _____ NO _____
3. GINGIVAL MUCOSA	YES _____ NO _____
4. BUCCAL MUCOSA	YES _____ NO _____
5. MUCOGINGIVAL MUCOSA	YES _____ NO _____
6. TONGUE	YES _____ NO _____
7. SUBLINGUAL AND SUBMANDIBULAR AREAS	YES _____ NO _____
8. SALIVARY GLANDS	YES _____ NO _____
9. TONSILAR AND PHARYNGEAL AREAS	YES _____ NO _____

IF ANSWER TO ANY OF QUESTIONS 1-9 IS "NO", PLEASE EXPLAIN

NAME OF DENTAL CLINIC _____

SIGNATURE OF EXAMINING DENTIST _____

FLORIDA DENTIST BOARD DENTIST CIVIL SERVICE EXAM FORM

Date _____ Subject Name _____ No. _____

Baseline

Mid-study

Final

UPPER TEETH

Tooth #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Facial Surface Score	X															
Lingual Surface Score	X															

LOWER TEETH

Tooth #	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17
Facial Surface Score	X															
Lingual Surface Score	X															

If tooth is missing, place **X** in score box

(See other side for Loe-Silness Gingivitis Scoring Procedure)

Name of Dental Clinic

Signature of Examining Dentist

PLAQUE EXAM FORM

Date _____ Subject Name _____ No. _____

Baseline

Mid-study

Final

UPPER TEETH																
Tooth #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Facial Surface Score	X															X
Lingual Surface Score	X															X

LOWER TEETH																
Tooth #	32	31	30	29	28	27	26	25	24	23	22	21	20	19	18	17
Facial Surface Score	X															X
Lingual Surface Score	X															X

If tooth is missing, place **X** in scorebox

(See other side for Modified Quigley-Hein Plaque Scoring Procedure)

Name of Dental Clinic

Signature of Examining Dentist

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APPENDIX VII
INTERIM VISIT FORM

SUBJECT'S INITIALS _____

SUBJECT NO. _____ DATE _____

1. Were there any unexpected or serious reactions since the previous examination? YES NO

If yes, describe _____

2. Was any treatment prescribed for above? YES NO

If yes, describe _____

3. Was any dental treatment received since previous examination? YES NO

If yes, describe _____

4. Was any medication prescribed for subject since previous examination? YES NO

If yes, describe dose, If yes, describe reason, dose, and duration

5. For female subject: Is subject pregnant or breast feeding an infant? YES NO

6. Do any of the responses to Questions 1-5 warrant exclusion of this subject's data from the statistical analysis? YES NO

If yes, explain _____

7. Will subject continue participation in the study? YES NO

If "no," complete Question 7 on Final Visit Form.

Examining Dentist Signature

Date

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APPENDIX VIII
FINAL VISIT FORM

SUBJECT'S INITIALS _____

SUBJECT NO. _____ DATE _____

1. Were there any unexpected or serious reactions since the previous examination? YES NO

If yes, describe _____

2. Was any treatment prescribed for above? YES NO

If yes, describe _____

3. Was any dental treatment received since previous examination? YES NO

If yes, describe _____

4. Was any medication prescribed for subject since previous examination? YES NO

If yes, describe dose, duration, and reason _____

5. For female subject: Is subject pregnant or breast feeding an infant? YES NO

6. Do any of the responses to Questions 1-5 warrant exclusion of this subject's data from the statistical analysis? YES NO

If yes, explain _____

7. Did subject complete the study? YES NO

If no, explain _____

Examining Dentist Signature

Date

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APPENDIX IX**

NOTE: SERIOUS ADVERSE EXPERIENCES MUST BE REPORTED IMMEDIATELY TO THE
CLINICAL RESEARCH DEPARTMENT, COLGATE-PALMOLIVE COMPANY, TELEFAX NUMBER
732-878-7084.

Product Name: _____

Study No. _____ Investigator: _____

Date of Report _____

Subject Number	Subject Initials	Sex	Age	Weight	Ethnic Group
Reaction (describe in detail)					
Date of onset	Duration to date	Onset Type (Gradual, Sudden, Unknown)	Severity (Mild, Moderate, Severe, Unknown)	Relationship to Product (Certain, Probable, Possible, Doubtful, Unknown)	
Length of time on product at onset			Randomization Group	Dose	
Medical history/concurrent illnesses/concomitant medications (give details):					
Treatment given for reaction (check one):					
None, continued in study					
None, discontinued from study					
Continued in study, given additional treatment (specify)					
Discontinued study, given additional treatment (specify)					

Signature of Investigator

Date

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APPENDIX IX

NOTE: This form is to be filled out at each study visit until the adverse experience has been resolved or until study participation ends.

Product Name: _____

Study No. _____ Investigator: _____

Subject Number	Subject Initials	Sex	Age	Date
Outcome of event to date (check one):				
Reaction has abated				
Reaction requires ongoing treatment (specify):				
Subject died:				
Date of death:				
Cause of death:				
Additional comments:				

Signature of Investigator

Date