FREEDOM OF INFORMATION SUMMARY

Original New Animal Drug Application

NADA 141-082

HESKA™ Periodontal Disease Therapeutic

"….for the treatment and control of
periodontal disease in dogs."

Sponsored by:

Heska Corporation
Fort Collins, Colorado

7/16/97

I. GENERAL INFORMATION

NADA Number: 141-082

Sponsor: Heska Corporation
1825 Sharp Point Drive
Fort Collins, Colorado 80525

Generic name: Doxycycline hyclate

Trade name: HESKA™ Periodontal Disease Therapeutic

Marketing status: A prescription product which carries the following caution statement: "Federal law restricts this drug to use by or on the order of a licensed veterinarian."

II. INDICATIONS FOR USE

The HESKA Periodontal Disease Therapeutic is indicated for the treatment and control of periodontal disease in dogs.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

The HESKA Periodontal Disease Therapeutic is provided in a two syringe system requiring mixing prior to use. Syringe A contains the polymer delivery system (*N*-methyl-2-pyrrolidone and poly(DL-lactide)) and Syringe B contains the active ingredient (doxycycline). Once mixed, the product is a flowable solution of doxycycline hyclate equivalent to 8.5% doxycycline activity. The formulation is applied subgingivally to the periodontal pocket(s) of affected teeth, and doxycycline is slowly released from the polymer providing a local antimicrobial effect. Use as many units as required to fill the periodontal pockets of affected teeth.

IV. EFFECTIVENESS

A. Dose Justification:

The dosage of 8.5% doxycycline (10% doxycycline hyclate) was selected because it is the maximal dosage of doxycycline that, when combined with the delivery system, maintains acceptable handling characteristics (syringeability) of the reconstituted product. As there were no concerns

related to the safety of the product based on either total dose of doxycycline or doxycycline concentration, the dosage was chosen to achieve the maximal possible concentration of doxycycline in the gingival crevicular fluid that would persist for the longest period.

B. Dose Confirmation in Naturally Occurring Periodontal Disease - ATS-65

1. Location: Inhausen Research Institute, Inc.
   Fort Collins, Colorado

2. Study Director - In-life Phase: Jon C. Fulfs, Ph.D., Inhausen
   Principal Investigator: Alan Polson, D.D.S., M.S., Atrix Laboratories

3. Objective: This study evaluated the efficacy of the 10% doxycycline hyclate (equivalent to 8.5% doxycycline) formulation in naturally occurring periodontal disease in dogs.

4. Animals: Five adult (5-10 years) female Beagle dogs with naturally occurring periodontal disease.

5. Controls: Each dog's baseline evaluation served as the control.

6. Dosage Form: 4 of the 5 dogs were treated with the final market formulation containing 10% doxycycline hyclate (equivalent to 8.5% doxycycline).

7. Route of Administration: Prior to test article adminstration, each dog was put under general inhalant anesthesia. The product was administered subgingivally (topically) in the periodontal pocket(s) of the affected tooth or teeth.

8. Dosage Used: Sufficient to fill the qualifying periodontal pockets.

9. Duration: Four of the dogs were evaluated for approximately four months (112-115 days); and one dog was euthanized after 39 days for pulmonary thrombosis and renal failure related to renal amyloidosis which was not attributed to drug administration.

10. Other Dental Treatments: Each dog's teeth were brushed with a commercially available toothpaste three times a week beginning after removal of the remaining polymer on Day 7.

11. Pertinent Parameters Measured:
    A. Daily clinical observations by qualified animal care personnel; test sites were observed daily through Day 7 for evidence of infection or other adverse reactions to the test article.
    B. Clinical measurements: Periodontal Pocket Depth, Attachment Level, Bleeding on Probing
    C. Subgingival plaque sample for total bacterial cell counts
    D. Polymer retention evaluation - absent vs. present

12. Results: No adverse reactions were observed after test article administration. Mean pocket depth measurements, mean attachment loss measurements and mean bleeding on probing scores were reduced by 14 days after treatment, and the reductions were essentially maintained through the remainder of the study (Table 1).

    Total bacterial counts were reduced within the first two weeks in all dogs studied. Gingival crevicular fluid concentrations of doxycycline exceeded the minimum inhibitory concentration of most periodontal pathogens. Polymer retention observations through Day 7 are summarized in Table 2.

    Table 1. Mean Pocket Depth, Attachment Level and Bleeding on Probing Scores for dogs (n = 4 dogs, 3 teeth/dog, 69 pockets).

Day	Mean PD[1]	Mean AL[2]	Mean BOP[3]
0	6.63	5.83	2.20
14	4.00	4.45	0.33
21	3.98	4.25	0.25
28	3.65	3.98	0.30
43†	3.85	3.95	0.45
57	4.00	3.73	0.47
73	3.90	3.57	0.33
86	3.90	3.53	0.47
93	3.83	3.33	0.50
112	3.67	3.20	0.53

[1]PD = Pocket Depth (mm)
[2]AL = Attachment Level (mm)
[3]BOP = Bleeding on Probing (scored 0-3: 0 for no bleeding; 1 for a single bleeding point or a fine line of blood; 2 if the interdental triangle or direct margin became filled with blood; 3 if profuse bleeding immediately after probing.)
† after Day 39, number of dogs = 3, number of pockets = 60, because one dog was euthanized.

Table 2. Mean retention of polymer through Day 7

Day	Percent retention
1	100%
3	91%
4	82%
5	83%
7	78%

13. Conclusions: This study demonstrated the efficacy of the 10% doxycycline hyclate (equivalent to 8.5% doxycycline) formulation in naturally occurring periodontal disease in dogs. The Periodontal Disease Therapeutic was effective in increasing attachment level and decreasing periodontal pocket depths for approximately 4 months after treatment. The product also decreased gingival inflammation as evidenced by decreased bleeding on probing scores. Total bacterial counts were decreased within two weeks in all dogs.

C. Dose Confirmation in Naturally Occurring Periodontal Disease - ATS-53

1. Location: Inhausen Research Institute, Inc.
   Fort Collins, Colorado

2. Study Director - In-life Phase: Jon C. Fulfs, Ph.D., Inhausen
   Principal Investigator: Alan Polson, D.D.S., M.S., Atrix Laboratories

3. Objective: This study evaluated the efficacy of the 10% doxycycline hyclate (equivalent to 8.5% doxycycline) formulation in naturally occurring periodontal disease in dogs.

4. Animals: Four adult (7-10 years) female Beagle dogs with naturally occurring periodontal disease.

5. Controls: Each dog's baseline evaluation served as the control.

6. Dosage Form: 10% doxycycline hyclate (equivalent to 8.5% doxycycline) formulation presented pre-mixed in a l ml polyethylene syringe.

7. Route of Administration: Prior to test article adminstration, each dog was put under general inhalant anesthesia. The product was administered subgingivally (topically) in the periodontal pocket(s) of the affected tooth or teeth.

8. Dosage Used: Sufficient to fill the qualifying periodontal pockets.

9. Duration: Dogs were evaluated for approximately 9 months.

10. Other Dental Treatments: Each dog's teeth were brushed with a commercially available toothpaste three times a week beginning after removal of the remaining polymer on Day 7.

11. Pertinent Parameters Measured:
    A. Daily clinical observations by qualified animal care personnel; test sites were observed daily through Day 7 for evidence of infection or other adverse reactions to the test articles.
    B. Clinical measurements: Periodontal Pocket Depth, Attachment Level, Bleeding on Probing
    C. Subgingival plaque sample for total bacterial cell counts
    D. Polymer retention evaluation - absent vs. present

12. Results: No adverse reactions attributed to the treatment were observed at the treatment sites. All sites selected to receive treatment were slightly to moderately inflamed from the pre-existing periodontal disease, and gingival inflammation and edema were common findings throughout the study. Analyses of variance at 9 months showed significant ($p<0.001$) differences among the mean responses across time for pocket depth, attachment level, and bleeding on probing. For pocket depth and bleeding on probing, all time points subsequent to baseline indicated mean reductions that were statistically significant (Table 3). For attachment level, statistically significant changes from baseline were shown at one month and at all later time points (Table 3). Polymer retention through Day 7 ranged from 33-83%.

Table 3. Mean Pocket Depth, Attachment Level and Bleeding on Probing Score for dogs (n=4; 3 teeth/dog)

Time	Mean PD[1]	Mean AL[2]	Mean BOP[3]
Baseline	6.10	4.93	2.43
2 weeks	4.13	4.15†	0.08
1 month	3.83	3.28	0.10
2 months	3.60	2.88	0.20
3 months	3.43	2.55	0.33
4 months	3.65	2.58	0.45
6 months	3.73	2.40	0.40
9 months	3.93	2.40	0.73

[1]PD = Pocket Depth (mm)
[2]AL = Attachment Level (mm)
[3]BOP = Bleeding on Probing (scored 0-3: 0 for no bleeding; 1 for a single bleeding point or a fine line of blood; 2 if the interdental triangle or direct margin became filled with blood; 3 if profuse bleeding immediately after probing.)
†Not significantly different from baseline; all other measurements were significantly different from baseline.

With treatment, an overall reduction in total bacterial cell counts was observed within two weeks and was maintained over the 9 month period following treatment, although the gingival crevicular fluid doxycycline concentration began to diminish a few days after treatment.

13. Conclusions: The Periodontal Disease Therapeutic was effective in increasing attachment level within one month, and the increase was maintained for 9 months after a single administration of the product. Periodontal pocket depth and bleeding on probing were significantly decreased within 2 weeks of treatment, and the decrease was maintained for 9 months. An overall reduction in total bacterial cell counts was observed within two weeks and was maintained over the 9 month period following treatment.

D. Evaluation of Vehicle in Naturally Occurring Periodontal Disease - ATS-58

1. Location: Inhausen Research Institute, Inc.
Fort Collins, Colorado

2 . Study Director - In-life Phase: Jon C. Fulfs, Ph.D., Inhausen
Principal Investigator: Alan Polson, D.D.S., M.S., Atrix Laboratories

3. Objective: This study evaluated the efficacy of the vehicle control formulation in naturally occurring periodontal disease in dogs.

4. Animals: Four adult (7 year old) female Beagle dogs with naturally occurring periodontal disease.

5. Dosage Form: Vehicle formulation consisting of 36.7% poly(DL-lactide) and 63.3% NMP.

6. Route of Administration: Prior to test article adminstration, each dog was put under general inhalant anesthesia. The product was administered subgingivally (topically) in the periodontal pocket(s) of the affected tooth or teeth.

7. Dosage Used: The volume of the vehicle solution (0% doxycycline) deposited around each tooth was sufficient to fill the qualifying periodontal pockets.

8. Duration: Dogs were evaluated for approximately 4 months.

9. Other Dental Treatments: Each dog's teeth were brushed with a commercially available toothpaste three times a week beginning after removal of the remaining polymer on Day 7.

10. Pertinent Parameters Measured:
    A. Daily clinical observations by qualified animal care personnel; test sites were observed daily through Day 7 for evidence of infection, inflammation or other adverse reactions to the test articles.
    B. Clinical measurements: Periodontal Pocket Depth, Attachment Level, Bleeding on Probing
    C. Subgingival plaque sample for total bacterial cell counts
    D. Polymer retention evaluation - absent vs. present

11. Results: No signs of toxicity were observed during or after the treatment period. All sites selected to receive treatment presented with inflammation and/or erythema at initial pre-screening examinations. During the seven-day treatment period, the test sites continued to present with inflammation and erythema.

    Statistical results of the clinical data revealed no clinically significant differences among the mean responses across time for pocket depth and attachment level (Table 4). Bleeding on probing was significantly reduced across time. Significant reductions in bleeding on probing were found at 2 weeks, 1 month and 3 months. Reductions for months 2 and 4 were not significant. The decrease in bleeding on probing may be related, in part, to the 3x/week dental hygiene. This study demonstrated that periodontal disease does not regress spontaneously.

Mean total bacterial cell counts were reduced from baseline within one week after treatment, and remained decreased thereafter. The decrease in bacteria may be related, in part, to the 3x/week dental hygiene. Polymer retention through Day 7 was approximately 42%.

Table 4. Mean Pocket Depth, Attachment level and Bleeding on Probing Score for dogs (n=4; 3 teeth/dog) treated with vehicle formulation

Time	Mean PD[1]	Mean AL[2]	Mean BOP[3]
Baseline	5.88	4.63	1.83
2 weeks	5.48	4.30	1.10†
1 month	5.28	4.13	0.93†
2 months	5.63	4.25	1.38
3 months	5.43	4.25	1.08†
4 months	5.55	4.33	1.45

[1]PD = Pocket Depth (mm)
[2]AL = Attachment level (mm)
[3]BOP = Bleeding on Probing (scored 0-3: 0 for no bleeding; 1 for a single bleeding point or a fine line of blood; 2 if the interdental triangle or direct margin became filled with blood; 3 if profuse bleeding immediately after probing.)
†Significantly different from baseline

12. Conclusions: This study demonstrated that the vehicle control formulation was safe for use in dogs with naturally occurring periodontal disease. The vehicle formulation did not alter attachment level or pocket depth. This study also demonstrated that periodontal disease does not spontaneously regress. While some effect on the bleeding on probing scores and number of periodontal pathogens was observed under conditions of this study (3x weekly brushing), the magnitude of reduction was less than in other studies involving the active product (doxycycline) under similar conditions.

E. Antibiotic Susceptibility of Canine Periodontal Pathogens - 81-002

1. Locations: Laboratory Animal Facilities, Colorado State University
Fort Collins, Colorado

Harmony Hospital for Pets
Fort Collins, Colorado

2. Study Directors: Susan L. Longhofer, D.V.M., M.S., Heska Corporation and Jerry White, D.V.M., Harmony Hospital for Pets

3. Objective: This study identified periodontal pathogens cultured from subgingival plaque of dogs with periodontal disease and determined the minimum inhibitory concentration (MIC) of doxycycline against these pathogens.

4. Animals: Dogs came from two locations; Group 1 consisted of 15 adult Beagle dogs, 11 intact females, 3 intact males and 1 castrated male, from a colony of dogs maintained in the Laboratory Animal Resources facilities at Colorado State University. Group 2 consisted of 15 client-owned dogs presented for dental prophylaxis to Harmony Hospital for Pets and included 6 spayed females, 2 intact males and 7 castrated males. Group 2 dogs represented a variety of breeds and ranged in age from 1.5 to 15 years old.

5. Controls, Dosage Form, Route of Administration, Dosage Used and Duration: Not applicable - no drug was administered in this trial. The 15 Beagle dogs received injectable intravenous anesthesia for periodontal culturing, and the 15 client-owned dogs received inhalant general anesthesia.

6. Pertinent Parameters Measured: Subgingival plaque samples were taken from each dog under general anesthesia. Aerobic and anaerobic isolates were obtained from one site from each dog and identified using commercial biochemical identification systems. The isolates were then tested for antibiotic susceptibility to doxycycline using agar dilution or broth microdilution MIC procedures.

7. Results: The majority of isolates were gram negative and anaerobic (*Campylobacter rectus* isolates were included as anaerobes). The most common species were *C. rectus* and gram positive bacillus strains that could not be definitively identified. These were followed by *Alcaligenes* species, *Fusobacterium* species, some gram negative anaerobic bacillus strains that could not be conclusively identified and *Porphyromonas* species. The majority of gram positive species were *Streptococcus.*

   These isolates (n= 183) were collected from 30 dogs, 15 of which were laboratory Beagles and the other 15 were client-owned dogs of different breeds.

   The MIC_{50} was $\leq$ 0.5 mcg/mL, and the MIC_{90} was 4.0 mcg/mL. When evaluating all isolates, doxycycline was demonstrated to be an effective antimicrobial for canine periodontal pathogens with 98.5% of the isolated organisms susceptible to concentrations $\leq$4 mcg/mL.

When isolates from canine dental specimens were tested against selected antimicrobials, the order of activity (from most to least active) was amoxicillin-clavulanate = doxycycline > enrofloxacin > metronidazole-spiramycin > cephalexin > cefadroxil > clindamycin > metronidazole.

The greater activity of doxycycline and amoxicillin-clavulanic acid reflects their wider spectrum of activity against both gram-positive and gram-negative bacteria. In Table 12, it is apparent that only 2 of the 8 drugs were >90% susceptible against all isolates, i.e. doxycycline and amoxicillin-clavulanic acid both with 98.5% of the strains susceptible to each antibiotic. The next most active drug was enrofloxacin with 81.2% of the strains susceptible to this antibiotic.

8. Conclusions: The most frequently isolated organisms in this study included: *Alcaligenes faecalis, Fusobacterium nucleatum, Porphyromonas gingivalis, Campylobacter rectus* and gram-positive, aerobic bacillus.

   When all isolates were tested, 98.5% of them were susceptible to doxycycline with an MIC_{50} of $\leq$ 0.5 mcg/mL and an MIC_{90} of <4 mcg/mL. When these isolates were tested against selected antimicrobials, the order of activity (from most active to least active) was amoxicillin-clavulanate = doxycycline > enrofloxacin > metronidazole-spiramycin > cephalexin > cefadroxil > clindamycin > metronidazole. The gingival crevicular fluid doxycycline concentrations measured during study ATS-53 were more than several fold higher than the MIC_{90}s of the pathogens isolated in this study, for several days. Based on these *in vitro* results, doxycycline should be used for the treatment of bacteria causing periodontal disease in dogs.

V. ANIMAL SAFETY

A . Safety and Bioactivity in Dogs with Naturally Occurring Periodontal Disease - ATS-32

1. Location: Inhausen Research Institute, Inc.
   Fort Collins, Colorado

2. Study Director - In-life Phase: Jon C. Fulfs, Ph.D., Inhausen

3. Objective: This study evaluated the tissue irritation potential and drug release into gingival crevicular fluid when the formulations were placed into naturally occurring periodontal pockets in the dog. The study also evaluated whether systemic blood concentrations of doxycycline were obtained after treatment with the subgingival (topical) formulation. This study was conducted according to Good Laboratory Practices.

4. Animals: Six adult, 20-33.5 lb. (9.1-15.2 kg), female Beagle dogs with naturally occurring periodontal disease.

5. Controls: For each dog, one site (periodontal pocket) was randomly assigned to serve as a control site. Control sites were lavaged with physiologic saline.

6. Dosage Form: 5% and 10% doxycycline hyclate formulations.

7. Route of Administration: Prior to test article adminstration, each dog was put under general inhalant anesthesia. The product was administered subgingivally (topically) in the periodontal pocket(s) of the affected tooth or teeth.

8. Dosage Used: The volume of the doxycycline solution deposited around each tooth was sufficient to fill the qualifying periodontal pocket. Three dogs each had five teeth selected for treatment (two teeth were treated with the 5% formulation; two teeth were treated with the 10% formulation and one site was used as a control site). An additional three dogs each had three teeth selected for treatment (one tooth was treated with the 5% formulation; one tooth was treated with the 10% formulation and one site was used as a control site).

9. Pre-treatment procedures: Selected teeth were subgingivally and supragingivally scaled and debrided prior to treatment.

10. Duration: The dogs were evaluated for 28 days.

11. Pertinent Parameters Measured:
    A. Clinical observations for toxicity, including evaluation of all treatment sites for edema or erythema, were made 3, 6, 12 and 24 hours after treatment administration, then daily for an additional 27 days. Dogs were observed for morbidity and mortality daily by qualified animal care personnel.
    B. Blood samples were obtained for doxycycline assay at 6, 12 and 24 hours, daily for six days and then on Days 10, 14, 21 and 28.

12. Results: Daily observations did not reveal any evidence of toxicity. Mild inflammation characterized by erythema and edema was present for approximately three days after treatment in treated and control sites and was attributed to the dental scaling procedure.

    Mean erythema scores were always less than or equal to 1 (very slight erythema [barely perceptible]) through Day 3 and only isolated observations yielding scores greater than zero were noted thereafter. Erythema in the first few days following treatment was similar in dogs receiving either active formulation, and appeared to be related to the physical trauma of the scaling and debridement procedures prior to the placement of the test articles. The control sites receiving only physiologic saline appeared to have slightly less erythema, probably because they did not receive the same degree of physical manipulation as the treated sites. Occasional observations of very slight erythema in two animals after Day 3 were considered by the study director to most likely be related to consumption (and chewing) of dry dog food.

    Mean edema scores were generally less than 1 (very slight edema [barely perceptible]) through Day 3 and no edema occurred thereafter through the end of the study. Edema ranged from very slight to moderate in individual dogs, was generally limited to the first few days after treatment, and was similar in dogs receiving either active formulation. Since control sites exhibited edema as well, it appeared to be directly related to the trauma of scaling and debridement.

    Detectable plasma doxycycline concentrations were present in the three dogs which had four treated sites, but only at 6 and 12 hours after treatment onset (Table 5).

Table 5. Plasma doxycycline in dogs treated with 5% and 10% doxycycline hyclate formulations

Dog #	# sites treated	Total dose (mg)*	Detectable doxycycline 0 hour	6 hour	12 hour	24 hour
FRG3	4	22.6	No	Yes	Yes	No
SKE4	4	13.7	No	Yes	Yes	No
XLE3	4	20.4	No	Yes	Yes	No
PLO2	2	4.7	No	No	No	No
QTW3	2	5.3	No	No	No	No
ZAQ2	2	6.6	No	No	No	No

*total dose of doxycycline = sum of weight of the formulation administered per test site (mg) X drug load (%)
No drug was detected in any plasma sample after 12 hours post-treatment

13. Conclusions: This study demonstrated the lack of tissue irritation of the product when the formulations were placed into naturally occurring periodontal pockets in the dog. The study also demonstrated that minimal systemic blood concentrations were obtained after treatment. Mild inflammation characterized by erythema and edema was present for approximately three days after treatment in treated and control sites and was attributed to the dental scaling procedure. No pattern of response was observed which could be related to the test articles and no dose-related gingival irritation was observed.

B. Safety in Dogs with Naturally Occurring Periodontal Disease - ATS-31

1. Location: International Research and Development Corporation Mattawan, Michigan

2. Study Director: Edwin I. Goldenthal, Ph.D.

3. Objective: This study evaluated the tissue irritation potential when formulations were placed into naturally occurring periodontal pockets in the dog. This study was conducted according to Good Laboratory Practices.

4. Animals: Twelve adult (6.5-10 years), 7.5-16.5 kg, female Beagle dogs with naturally occurring periodontal disease.

5. Controls: For each dog, at least two sites (periodontal pockets) were selected to serve as control sites. Control sites were lavaged with physiologic saline.

6. Dosage Form: 5% and 10% doxycycline hyclate formulations.

7. Route of Administration: Prior to test article adminstration, each dog was put under general inhalant anesthesia after an injectable premedicant was administered intravenously. The product was administered subgingivally (topically) in the periodontal pocket(s) of the affected tooth or teeth.

8. Dosage Used: The volume of the doxycycline solution deposited around each tooth was sufficient to fill the qualifying periodontal pocket(s). Two groups of six animals each were treated with either the 5% or 10% doxycycline hyclate formulations. Each dog had four teeth selected for treatment. Two teeth were treated with the appropriate test formulation (either 5% or 10% doxycycline hyclate), and two teeth were used as control sites. One test periodontal pocket per dog was sealed with Iso Dent® (a cyanoacrylate adhesive) over top of the doxycycline solution which was placed in the periodontal pocket. One control periodontal pocket per dog was also sealed with Iso Dent®.

9. Pre-treatment procedures: Selected teeth were subgingivally and supragingivally scaled prior to treatment.

10. Duration: The dogs were evaluated for 7-28 days. For each formulation, three dogs were designated for sacrifice after 7 and 28 days of study.

11. Pertinent Parameters Measured:
    A. Clinical observations for toxicity, including evaluation of all treatment sites for edema, erythema or other irritation were made periodically for approximately 4 hours after placement and twice daily thereafter.
    B. Dogs were necropsied for complete postmortem examination and histopathological examination 7 or 28 days after treatment administration.

12. Results: Emesis was noted in the cage of one dog (treated with 5% doxycycline) at 2 and 4 hours after treatment administration. The finding was attributed to anesthetic recovery. There were no other visible abnormalities in any dog during the study.

    Irritation, as evidenced by edema or erythema, was observed in the control sites, both sealed and unsealed, as well as the sites treated with the test articles. Tan and/or off-white material which could be either the Iso Dent or the polymer was seen in several gingival pockets. No tissue reaction was seen at these sites. At post-mortem examination no test article-related macroscopic lesions were evident in gingival test sites in dogs after 7 or 28 days of treatment. Histopathologically,

gingival irritation (related to the underlying periodontal disease) was seen in all treated sites, including the saline-treated sites. The animals sacrificed at Day 7 exhibited chronic gingivitis generally graded as moderate to severe. Six sites in the saline treated dogs, 5 sites in the 5% polymer treated dogs, and 3 sites in the 10% polymer treated dogs showed microscopic signs of severe, chronic gingivitis. Two saline treated, and two 10% polymer treated sites showed evidence of mild chronic gingivitis. By Day 28, the chronic gingivitis had been reduced to mild levels in most animals at all sites. One site in the saline treated dogs, 1 site in the 5% polymer treated dogs, and 3 sites in the 10% polymer treated dogs showed microscopic evidence of severe, chronic gingivitis. Eight saline treated, four 5% polymer treated, and two 10% polymer treated sites showed mild, chronic gingivitis on microscopic examination. The microscopic and macroscopic incidence of gingivitis was comparable between the 5% and 10% formulations and the control sites.

13. Conclusions: This study demonstrated the lack of tissue irritation when the test articles were placed into naturally occurring periodontal pockets in the dog. There did not appear to be any significant differences between the saline control and the two polymer concentrations when evaluated grossly and microscopically for gingival irritation.

VI. HUMAN SAFETY

Data on human safety, pertaining to drug residues in food, were not required for approval of this NADA. The drug is labeled for use in dogs, which are non-food animals.

VII. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of section 512 of the Act and section 514 of the implementing regulations. The data demonstrate that the HESKA™ Periodontal Disease Therapeutic (doxycycline hyclate), when used under labeled conditions, is safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical for the diagnosis of periodontal disease in dogs and for the safe use of the product.

Under section 512(c)(2)(F)(i) of the FFDCA, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval because no active ingredient (including any ester or salt of the active ingredient) has been approved in any other application.

The Heska Periodontal Disease Therapeutic is protected by the following patents:

Patent Number B1 4,938,763 - (exp.2/2008)
Patent Number 5,077,049 - (exp. 7/2009)
Patent Number 5,278,201 - (exp. 1/2011)
Patent Number 5,324,519 - (exp. 6/2011