Approval Date: December 23, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 055-099

B. Sponsor

Pfizer Inc.
235 East 42nd Street
New York, New York 10017

C. Proprietary Name

Clavamox® Tabs

D. Established Name

amoxicillin trihydrate/clavulanate potassium

E. Dosage Form

Tablet

F. Dispensing Status

Rx

G. Dosage Regimen

Dogs:
The recommended dosage is 6.25 mg (5.0 mg amoxicillin trihydrate/1.25 mg clavulanate potassium)/lb of body weight twice a day. Skin and soft tissue infections such as abscesses, cellulitis, wounds, and superficial/juvenile pyoderma and periodontal infections should be treated for 5-7 days or for 48 hours after all symptoms have subsided. If no response is seen after 5 days of treatment, therapy should be discontinued and the case reevaluated. Deep pyoderma may require treatment for 21 days; the maximum duration of treatment should not exceed 30 days.

Cats:
The recommended dosage is 62.5 mg (50.0 mg amoxicillin trihydrate/12.5 mg clavulanate potassium) twice a day. The duration of treatment should be 48 hours after all symptoms have subsided, not to exceed 30 days. If no response is seen after 3 days of treatment, therapy should be discontinued and the case reevaluated.

H. Route of Administration

Oral

I. Indication

Clavamox Tabs are indicated in the treatment of:

Dogs:
Skin and soft tissue infections such as wounds, abscesses, cellulitis, superficial/juvenile and deep pyoderma due to susceptible strains of the following organisms: ß-lactamase-producing *Staphylococcus aureus*, non-ß-lactamase-producing *Staphylococcus aureus*, *Staphylococcus* spp., *Streptococcus* spp., and *E. coli*.

Periodontal infections due to susceptible strains of aerobic and anaerobic bacteria. Clavamox® has been shown to be clinically effective for treating cases of canine periodontal disease.

Cats:
Skin and soft tissue infections such as wounds, abscesses, and cellulitis/dermatitis due to susceptible strains of the following organisms: ß-lactamase-producing *Staphylococcus aureus*, non-ß-lactamase-producing *Staphylococcus aureus*, *Staphylococcus* spp., *Streptococcus* spp., *E. coli*, and *Pasteurella* spp.

Urinary tract infections (cystitis) due to susceptible strains of *E. coli.*

Therapy may be initiated with Clavamox® prior to obtaining results from bacteriological and susceptibility studies. A culture should be obtained prior to treatment to determine susceptibility of the organisms to Clavamox®. Following determination of susceptibility results and clinical response to medication, therapy may be reevaluated.

J. Effect of Supplement

Provides for additional claim against canine periodontal infections due to susceptible strains of aerobic and anaerobic bacteria.

II. EFFECTIVENESS

Data demonstrating the effectiveness of Clavamox® Tabs for previously approved indications are discussed in the parent NADA 55-099 FOI Summary (approval date November 9, 1984). The clinical efficacy and safety of Clavamox Tablets in dogs for the treatment of periodontal infections caused by aerobic and anaerobic bacteria are evaluated in the following studies.

A. Efficacy

Study No. AU-G 5000-94

1. **Type of Study:**

   Clinical

2. **Investigator:**

   Colin E. Harvey, BVSc, FRCVS, DipACVS, DipAVDC, Veterinary Hospital of the University of Pennsylvania (VHUP), Philadelphia, PA

3. **General design:**

   a. **Purpose:**

      This study was specifically designed to:

      (i) Identify the aerobic and anaerobic organisms present in the oral cavity of the clinically affected animals enrolled in the study. The presence of these organisms is a contributing factor to the development of periodontal disease.

      (ii) Demonstrate the clinical efficacy of Clavamox Tablets compared to placebo for the treatment of animals exhibiting the clinical signs associated with the early stages of gingivitis and periodontal disease. This primary gingival disease is a stage of the disease which would be responsive to antibiotic therapy alone, a process without bony involvement or excessive amounts of calculus which would add to the gingival irritation at the gingival margin. Periodontal disease, left untreated, is a progressive condition that will eventually result in involvement of underlying bony tissue and supporting periodontal soft tissues.

      (iii) Demonstrate that Clavamox Tablets are safe when used in a clinical setting for the treatment of primary gingival disease.

   b. **Treated**: 18 dogs treated with Clavamox® Tablets.

   c. **Controls**: 18 dogs received a placebo.

   d. **Diagnosis**: Pre-treatment bacterial cultures were performed to identify the bacteria that were associated with the disease state. Susceptibility data were reported for representative samples of the organisms isolated, which were defined as the two most predominant organisms of different genus and species, isolated from each animal. Both aerobic and anaerobic culture media were used.

   e. **Dosage form**: Tablet.

   f. **Route of Administration**: Oral.

   g. **Dose**: Clavamox® was dosed at the label dosage of 6.25 mg/lb body weight twice daily.

   h. **Test duration**: Treatment was administered orally for a minimum of 7 days and a maximum of 10 days.

   i. **Pertinent parameters measured**: Enrolled animals received a pre-treatment evaluation consisting of:

      (1) a general physical examination to determine the animal's general health and diagnose the presence of gingivitis;
      (2) collection of blood for a complete blood cell count (CBC) including a differential and clinical chemistry evaluation to assist the investigator in assessing the animal's general health;

(3) microbiologic culture and sensitivity of the gingival sulcus to identify the organisms contributing to the disease process;
(4) identification of clinical evidence of gingivitis including gingival inflammation, edema, bleeding, halitosis and periodontal pocket formation; and
(5) indexing of the clinical signs of gingivitis, including the gingival index, calculus index, plaque index and furcation index.

The gingival index was graded on a scale of 0-3, where 0 = normal gingiva and 3 = severe inflammation marked by redness and edema, ulceration could be present, and there could be spontaneous bleeding in addition to bleeding on probing. The calculus index was graded on a scale of 0-3, where 0 = no calculus seen or felt, and 3 = an abundance of supra-gingival and sub-gingival deposit. The plaque index was graded on a scale of 0-3 with 0 = no plaque in the gingival area, and 3 = abundant soft matter in the pocket or at the free gingival margin. The furcation index was graded on a scale of 0-3 also, with 0 = no furcation exposure, and 3 = the probe could be extended all the way through the exposed root. Also (6) recording of the periodontal pocket depth of the left and right upper canine teeth, left and right upper fourth pre-molars and left and right upper first molars was taken.

The post-treatment examination was conducted as soon as possible after the last day of treatment, but not longer than 2 days after cessation of therapy. The post-treatment evaluation included:

(i) a physical examination;

(ii) identification of the clinical evidence of gingivitis including gingival inflammation, edema, bleeding, halitosis and periodontal pocket formation;

(iii) indexing of the clinical signs of gingivitis, including the gingival index and plaque index and recording of the periodontal pocket depth of the left and right upper canine teeth, left and right upper fourth pre-molars and left and right upper first molars. The pre and post-treatment pocket depths were summed for an overall look at the change in periodontal pocket depth as a measure of oral health as well as looking at the change in each pocket depth individually. In addition,

(iv) recording of a clinical (therapeutic) result, as defined in the protocol on the basis of the change in the gingival index from pre-treatment to post-treatment evaluation was recorded; and

(v) documentation of any adverse effects observed during the treatment and post-treatment periods was made.

4. **Results:**

The most frequent organisms isolated from the 36 cases enrolled in the study included: *Alcaligenes faecalis/odorans*, *Escherichia coli*, *Pasteurella multocida*, *Streptococcus mutans* and gram-negative, aerobic rods. Seventy-three of the 77 organisms (94.8%) subjected to sensitivity testing were sensitive to

Clavamox.

None of the animals was graded a clinical (therapeutic) failure on the basis of the change in gingival index from pre-treatment to post-treatment. This was not unexpected considering the early stage of the disease process required by the protocol. However, no difference was detected between the two treatments on the basis of the protocol defined clinical (therapeutic) result grade i.e. whether the progression of clincial signs of gingivitis from pre to post-treatment were reversed, arrested.

Periodontal pocket depth was measured before and after treatment for 6 teeth: the canine tooth, fourth pre-molar and first molar in both the upper right and upper left arcades. The sum of the periodontal pocket depths was used to indicate the overall periodontal health of the oral cavity. The change observed in the sum of the pocket depths both pre and post-treatment represented a stasis, worsening or improvement in the overall disease process as a result of treatment.

The overall effect of treatment on the periodontal health of the oral cavity favored Clavamox®-treated animals at 2.08 mm over placebo-treated animals at 0.42 mm ($p < 0.05$). This more favorable effect was also apparent at the level of the individual teeth measured. In addition, the estimated overall reduction in periodontal pocket depth demonstrated a trend in favor of Clavamox® therapy vs placebo medicated controls as improvement occurred in the entire Clavamox® population ($p=.002$) as opposed to no overall improvement in the latter ($p=0.41$) when compared to zero (i.e. no change).

No adverse effects were noted in any of the dogs treated with Clavamox® Tabs.

5. **Statistical methods: The response variables that were measured and analyzed were:**

   a. temperature [F°]

   b. pulse [beats/minute]

   c. respiration [breaths/minute]

   d. clinical evaluation

   e. Tooth pocket depths [mm]:

   f. Left upper arcade (LUA) canine

   g. LUA 4th premolar

   h. LUA 1st molar

   i. Right upper arcade (RUA) canine

   j. RUA 4th premolar

   k. RUA 1st molar

Overall pre-treatment, overall post-treatment, reduction, and overall reduction in tooth pocket depth were calculated for each animal where:

- overall pre-treatment tooth pocket depth=$^{6}\text{Sigma}_{i=1}\text{alpha}_i$ where alpha_i=pre-treatment pocket depth of tooth i.
- overall post-treatment tooth pocket depth=$^{6}\text{Sigma}_{i=1}ß_i$ where $ß_i$=post-treatment pocket depth of tooth i.
- reduction of tooth i=alpha_i-$ß_i$
- overall reduction in tooth pocket depth=$^{6}\text{Sigma}(\text{alpha}_{i,\ i=1}\text{-}ß_i)$

Protocol evaluation of success was determined for each animal. A success was defined as a reduction in gingival index between pre-treatment and post-treatment values. Arrest of disease was defined as no change in gingival index, and a failure was defined as an increase in gingival index.
Data were recorded on data capture forms provided by Pfizer Animal Health. Data collected were analyzed by Biometrics and Information Services, Pfizer Animal Health, Lee's Summit, Missouri. The data were analyzed with either a general linear models procedure or a mixed models procedure (SAS/STAT User's Guide, SAS Institute, Cary, NC).

6. **Conclusions:**

   a. The microorganisms isolated from the clinical cases enrolled in the study include gram-positive, aerobic coccoid microbes as well as gram-negative, rod shaped, anaerobic flora.

   b. The microbes associated with the development of gingivitis and periodontal disease are susceptible to Clavamox (amoxicillin trihydrate/clavulanate potassium).

   c. In clinical cases in the early stages of gingivitis and periodontal disease without underlying bony involvement, Clavamox was more effective than placebo at reversing and/or halting the progress of the disease.

   d. Clavamox is a safe treatment when administered to clinically affected animals.

B. Efficacy

Study AU-G 5001-94

1. **Type of Study: Clinical**

2. **Investigators:**

   Edward Eisner, , DVM, Dipl AVDC, Denver, CO
   Gary Goldstein, DVM, Dipl AVDC, Houston, TX
   Steven Holmstrom, DVM, Dipl AVDC, Belmont, CA
   Charles Williams, DVM, Dipl AVDC, Fairfax, VA
   Robert B. Wiggs, DVM, Dipl AVDC, Dallas, TX
   Benjamin Colmery III, DVM, Dipl AVDC, Southfield, MI

3. **General design:**

   a. **Purpose**:

This study was specifically designed to:

1) Demonstrate the clinical efficacy of Clavamox compared to an approved product as positive control, Antirobe (clindamycin hydrochloride; Pharmacia Upjohn), for the treatment of animals exhibiting the clinical signs of gingivitis associated with periodontal disease. The study was designed to include those animals with the severity of periodontal disease that is typically treated in small animal clinical practice and allow for concurrent therapeutic procedures (i.e. subgingival and supragingival dental scaling) that is routinely incorporated in the treatment regimen for this condition.

2) Demonstrate that Clavamox is safe when administered in a clinical setting for the treatment of canine gingival and periodontal disease.

b. **Treated**: 42 dogs treated with Clavamox.

c. **Controls**: 50 dogs treated with Antirobe capsules (clindamycin hydrochloride; Pharmacia Upjohn)

d. **Diagnosis**: Based on clinical signs (hypersalivation, halitosis), an indexing of clinical signs of gingivitis associated with periodontal disease including periodontal pocket depth, and gingival index.

e. **Dosage form**: Tablet

f. **Route of administration**: Oral

g. **Dose**: Both products were dosed at the label doses: Clavamox tablets at 6.25 mg/lb body weight twice daily and Antirobe capsules at 2.50 mg/lb body weight twice daily.

h. **Test duration**: Treatment was administered for a minimum of 7 days and a maximum of 10 days.

i. **Pertinent parameters measured**: Enrolled animals received a pre-treatment evaluation consisting of the same parameters as was done for the previous study AU-G 5000-94, with one exception; no microbiologic cultures were taken of the gingival sulci.

j. The post-treatment examination and evaluation were conducted as soon as possible after the last day of treatment, but not longer than 2 days after cessation of therapy, and included evaluation of the same parameters as in the previous study AU-G 5000-94.

4. **Results:**

None of the animals was graded a clinical (therapeutic) failure on the basis of the change in gingival index from pre-treatment to post-treatment, indicating that both treatments resulted in stasis or reversal of the disease process in all of the animals treated; differences between treatment groups were non-significant ($p>0.05$). Periodontal pocket depth was measured before and after treatment for 6 teeth: the canine tooth, fourth pre-molar and first molar in both the upper right and upper left arcades. A sum of the periodontal pocket

depths measured at both evaluation times was taken to indicate the overall periodontal health of the oral cavity. Clavamox treatment was numerically improved over Antirobe when each of these measurements was used to evaluate efficacy, with a larger numeric reduction in mean pocket depth for Clavamox treated animals (1.24 mm) versus Antirobe treated dogs (0.44 mm). However, these differences were not significantly different (p= 0.15).

No adverse effects were noted in any of the dogs treated with Clavamox® Tabs.

5. **Statistical methods:**

   The response variables that were measured and analyzed were the same as those in the previous study AU-G 5000-94.

6. **Conclusions:**

   a. Both Clavamox and Antirobe treatment improved the overall periodontal health of the oral cavity and in many cases reversed the periodontal disease process.

   b. Clavamox was as effective as Antirobe at treating canine gingivitis and periodontal disease as measured by the reduction in periodontal pocket depth of the upper left (p=0.81) and right (p=0.41) canine teeth, upper left (p=0.23) and right (p=0.16) fourth pre-molars, upper left (p=0.10) and right (p=0.40) first molars and the sum of these periodontal pocket depths (p=0.15).

III. TARGET ANIMAL SAFETY

Studies AU-G 5000-94 and AU-G 5001-94 demonstrated the safety of Clavamox® for use in clinical cases of canine periodontal infections associated with aerobic and anaerobic infections. Safety for all other indications was established in the FOI Summary for Clavamox® Tablets NADA 55-099, (approval date November 9, 1984).

IV. HUMAN FOOD SAFETY

Human Safety Relative to Food Consumption:

Data on human food safety, pertaining to consumption of drug residues in food, were not required for approval of this supplemental NADA. Clavamox® is approved for use in dogs and cats only.

Human Safety Relative to Possession, Handling and Administration:

Labeling contains adequate caution/warning statements.

V. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of section 512 of the Act and Part 514 of the implementing regulations. The data demonstrate that Clavamox® Tabs (Amoxicillin trihydrate / clavulanate potassium), when used under labeled conditions of use are 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 infections

and for the safe use of the product.

Under section 512(c)(2)(F)(iii) of the Federal Food Drug and Cosmetic Act, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, or any studies of animal safety, required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the treatment of periodontal infections caused by susceptible strains of aerobic and anaerobic bacteria for which the supplemental application was approved.

The following patent numbers apply to NADA #55-099 for Clavamox® Tablets:

Patent #	**Expiration date**
4367175	01/04/2000
4441609	04/10/2001
4525352	06/25/2002
4529720	07/16/2002
4560552	12/24/2002

VI. ATTACHMENTS

Revised package insert

Copies of applicable labels may be obtained by writing to the:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.