CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-751

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

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CATEGORICAL EXCLUSION GRANTED.

(SEE CHEM. REVIEW# 2)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-751

PHARMACOLOGY REVIEW(S)

NDA 50-751

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Review and Evaluation of Pharmacology and Toxicology Data Division of Dermatologic and Dental Drug Products (HFD-540)

SEP 29 1997

Norman A. See, Ph.D., R.Ph.
Draft Completed: 9/24/97

Original Summary
Submission Date: 3/31/97
Center Receipt Date: 4/1/97

Sponsor: Atrix Laboratories, Inc.

Drug: Atridox®; Doxycycline hyclate periodontal gel

Formulation: Atridox® is a bio-erodible gel that, when placed within a periodontal pocket, provides sustained-release of doxycycline into the gingival crivicular fluid. The product is packaged as a "pro-product", consisting of two syringes, labeled "A" and "B". Syringe A contains 450mg of a vehicle ("Atrigel® Delivery System") that is composed of 36.7% poly(DL-lactide) (PLA) and 63.3% N-methyl-2-pyrrolidone (NMP). Syringe B contains doxycycline hyclate powder equivalent to 42.5mg of doxycycline base. The product is formed by mixing the contents of syringes A and B, yielding 500mg of a viscous yellow liquid (Atridox®) with a concentration of 8.5% w/w doxycycline base.

Maximum Proposed Dosage: Although a maximum dosage is not clearly indicated in the draft label, the reviewing Dental Officer (Dr. Kelsey) has suggested that 1 gram of Atridox® per treatment episode, possibly repeated at intervals of 4 months, be regarded as the maximum dose that a given patient might receive. This would result in per-treatment exposure to approximately 100mg of doxycycline hyclate, 330mg of PLA, and 570mg of NMP (2mg/kg, 6.6mg/kg, and 11.4mg/kg, respectively, in a 50kg individual).

Proposed Indication: Chronic adult periodontitis

Related Drugs/INDs/NDAs: IND

Table of Contents: **Page**

1. Pharmacodynamics. Doxycycline hyclate is an antibiotic compound with activity against many species of bacteria when administered at sufficient dosage. Please see the approved label for NDA 50-006 (Vibramycin) for a list of the species against which doxycycline has been proven to be effective. Presumably, antimicrobial activity accounts for the action of Atridox® in the treatment of periodontitis.

2. ADME, Pharmacokinetics. The pharmacokinetics of doxycycline have not been studied in animals under the IND that led to this NDA (IND . However, the "ADME" properties of doxycycline have been investigated and published[1]. Doxycycline is generally well absorbed from the GI tract, although aluminum-containing antacids will interfere with absorption. The extent of protein binding is variable, ranging from %. Published values for the serum half-life and renal clearance of doxycycline are hours and ml/min., respectively. The primary route of elimination of doxycycline is excretion in the bile; elimination of doxycycline is apparently not compromised by renal dysfunction. Please see section 3.1.6 of this review for discussion of doxycycline levels in the gingival crivicular fluid (GCF) or serum following placement of material similar to Atridox® within a periodontal pocket.

[1]American Hospital Formulary Service, American Society of Hospital Pharmacists, Washington, D.C.

3. Toxicology.

3.1 Single Dose Toxicolgy Studies.

3.1.1. A research pilot study to evaluate the clinical potential, safety, release characteristics, and biocompatibility of a 5% doxycycline hyclate formulation in Atrigel, study No. ATS-50, in-life 4/92-9/92, report dated 2/16/95, conducted by , exempted from compliance with Good Laboratory Practice regulations (21 CFR 58) as an exploratory pilot study.

This study was conducted to evaluate the biocompatibility and drug release properties of a test article that contained % (w/w) NMP, % PLA, and % (w/w) doxycycline hyclate. The test material was placed into periodontal pockets of four 7 to 10 year old beagle dogs. The test material was removed from the placement sites seven days after treatment. Paper strips were used to sample the GCF (fluid inside the periodontal pocket, surrounding the test material), which was analyzed for drug concentration and bacterial content. Samples of GCF were collected daily for the first two weeks following placement of the gel, and periodically thereafter until five months after treatment.

Results. The concentration of doxycycline in the GCF reached maximum on the day of application, and declined to zero over approximately seven days. Most of the solidified product was spontaneously lost from the periodontal pockets within seven days of placement, although it was still present at a few sites on the scheduled day of removal (day seven). The "periodontitis" of the dogs apparently improved slightly during the five month observation period, as suggested by slight improvements in the means of the pocket depths, clinical attachment level, and bleeding index. The microbiological data were not interpretable because baseline measurements had not been obtained, making it impossible to determine if the levels had changed. No adverse reactions or signs of toxicity were observed.

Conclusion. Under the conditions of this study, the test material released doxycycline within the periodontal pocket for several days, and the clinical status of the gingiva improved. It is unclear whether or not the treatment altered the oral flora.

3.1.2. A fourteen day study in dogs to evaluate the clinical potential, safety, bioactivity, and efficacy of 10% doxycycline hyclate formulations in Atrigel, study No. ATS-53, in-life 5/92-1/93, report dated 11/18/94, conducted by exempted from compliance with Good Laboratory Practice regulations (21 CFR 58) as an exploratory pilot study.

This study was conducted to evaluate the safety,

bioactivity, and "clinical applicability" of two formulations of Atrigel that both contained % doxycycline hyclate but which differed in terms of viscosity. One of the test articles (test article 1; lot# KSP-204-30-1) contained % (w/w) NMP, % (w/w) PLA; viscosity dL/g), and % (w/w) doxycycline hyclate. The other test article (test article 2; lot# KSP-204-30-2) contained % (w/w) NMP, % (w/w) PLA; viscosity dL/g)), and % (w/w) doxycycline hyclate. Each test article was placed into periodontal pockets of two 7 to 10 year old beagle dogs. The test material was removed from the placement sites seven days after treatment. Paper strips were used to sample the GCF, which was analyzed for drug concentration and bacterial content. Samples of GCF were collected daily for the first two weeks following placement of the gel (monitored for doxycycline concentration), and periodically thereafter until day 258 following treatment (monitored for bacterial count). The efficacy of the gels was assessed by monitoring pocket depth, clinical attachment level, and the amount of bleeding that occurred after probing the gingiva; these parameters were assessed periodically until termination of the study (nine months after treatment). The animals were not sacrificed at termination; necropsy and histopathology were not performed.

Results. The concentration of doxycycline in the GCF reached maximum within one day of application, and declined to zero by day 10. The more viscous formulation (lot# KSP-204-30-2) exhibited somewhat better retention at the site of application, being present in 5 of 6 treated sites on the seventh day following application, while the less viscous formulation was present at only 2 of 6 sites. All treated sites exhibited "marked improvement in periodontal clinical status", including reduction in pocket depth, increase in attachment level, and a reduction in bleeding-on-probing. These effects were observed within two to four weeks after treatment, and were maintained throughout the nine month observation period. GCF bacterial counts were also reduced. No adverse reactions or signs of toxicity were observed.

Conclusion. Under the conditions of this study, both formulations that were tested appeared to be equally efficacious. No adverse reactions or signs of toxicity were observed.

3.1.3. The evaluation of an Atrigel vehicle control formulation in periodontal pockets in the dog - a research exploratory study, study No. ATS-58, in-life 10/92-1/93, report dated 11/18/94, conducted by
exempted from compliance with Good Laboratory Practice regulations (21 CFR 58) as an exploratory pilot study.

The goal of this study was to assess a formulation of the vehicle used in Atridox® in terms of safety and efficacy following placement in periodontal pockets of aged dogs. The

test article (vehicle) contained % (w/w) NMP and % (w/w) PLA, viscosity dL/g (no doxycycline). The test article was placed into periodontal pockets of four 7 to 10 year old beagle dogs. The test material was removed from the placement sites seven days after treatment. Paper strips were used to sample the GCF, which was analyzed for bacterial content. The efficacy of the test article was assessed by monitoring pocket depth, clinical attachment level, and the amount of bleeding that occurred after probing the gingiva; these parameters were assessed periodically until termination of the study (four months after treatment). The animals were not sacrificed at termination; necropsy and histopathology were not performed.

Results. The treated sites exhibited slight improvement in periodontal clinical status, although much less than was observed with Atrigel that contained doxycycline hyclate in study ATS-53 (see section 3.1.2, above). No adverse reactions or signs of toxicity were observed.

Conclusion. These data suggest that under the conditions of this study the vehicle used in Atridox® is not toxic and that the vehicle alone may be slightly efficacious in the treatment of periodontitis.

3.1.4. Evaluation of Atrigel A/B delivery system for doxycycline hyclate in periodontal pockets in the dog. A research/exploratory study, study No. ATS-65, in-life 4/93-9/93, report dated 3/2/95, conducted by exempted from compliance with Good Laboratory Practice regulations (21 CFR 58) as an exploratory pilot study.

This study was conducted to evaluate the safety, bioactivity, and "clinical applicability" of a formulation of Atrigel that contained 8.5% doxycycline hyclate (the current formulation of Atridox®). The design of the study was similar to the designs of the studies that were summarized above. As in the studies summarized above, the test article was placed in periodontal pockets of aged dogs. This treatment appeared to improve the clinical status of the animals, as evidenced by reduction in pocket depth, increase in attachment level, and a reduction in bleeding-on-probing. No adverse reactions or signs of toxicity were observed.

3.1.5. Evaluation of gingival irritation and/or pathological effects in hard tissues in naturally occurring periodontal pockets in dogs, study No. 558-024, ATS-31, in-life 11/89, conducted by in compliance with Good Laboratory Practice regulations (21 CFR 58).

Two groups of adult female Beagle dogs (6 males and 6 females per group) were randomized to receive formulations of Atrigel that contained either % doxycycline hyclate; the formulations were:

Component	Weight % in Formulation	
Doxycycline Hyclate	5%	10%
PLA	%	%
NMP	%	%

Four naturally occurring periodontal pockets with a depth of mm were selected in each dog; the test sites were cleaned while the animals were anesthetized. While the animals were anesthetized, a syringe was used to fill two pockets in each animal with the assigned gel; the remaining two pockets were flushed with saline (controls). The amounts of test material deposited per site varied from mg in animals that received 5% gel and from mg in animals that received 10% gel. In each animal, one test and one control pocket were sealed with Iso Dent adhesive to (theoretically) increase retention of the injected material. The animals were observed twice daily until sacrifice; 3 dogs in each treatment group were killed on day 7 and 3 were killed on day 28. Each test site was examined grossly for erythema, edema (both assessed according to a standardized Draize technique on a scale of 0 to 4), and other signs of irritation twice daily. A postmortem examination, including the oral tissues, was performed at the time of sacrifice. Gingiva, bone, and tooth dentin from each of the application sites in each animal were examined.

Results.

Macroscopic pathology. Slight erythema and edema were initially observed in several animals from each of the control, 5%, and 10% treatment groups; the erythema generally cleared within 3 to 7 days. The observed slight erythema and edema probably resulted from the cleaning and treatment procedures. Sites sealed with Iso Dent were similar in appearance to those not sealed. No treatment-related lesions were observed at the test sites at the times of sacrifice (7 and 28 days).

Microscopic pathology. No apparent histopathologic differences between the groups were observed.

Conclusion. These data suggest that the test products were not substantially irritating under the conditions of the study.

Reviewer's comments: *It should be noted that this was not a typical oral mucosa irritation (OMI) study. However, the study design, which was similar to the proposed clinical use, would probably yield data that were more clinically relevant than would a typical OMI study. I assume that the periodontal pockets in these dogs were similar in etiology and histology to periodontal*

pockets in the clinical population. Since the test material is not intended to directly contact the oral mucosa and has been used in humans without serious adverse events, I consider a standard OMI study in which the gels were repeatedly applied to intact and abraded oral mucosa to be unnecessary. The fact that the test material apparently solidifies on contact with saliva would probably make a standard OMI study technically difficult if not unfeasible.

3.1.6. Evaluation of polymer formulations containing doxycycline hyclate for gingival tissue irritation, drug release and for blood drug levels following placement in canine periodontal pockets, study No. 128.002, ATS-32, in-life 11/89, conducted at in compliance with Good Laboratory Practice regulations (21 CFR 58). Note: According to a review of GLP EIR written by Manfred M. Hein of compliance (HFD-345, review dated 2-JUL-92) in regard to a similar study conducted at the same time and location for Atrix Labs., Inc. (study No. 128.001), and submitted to IND a 1990 inspection of listed the following deficiencies: A) two animals were mis-identified in the raw data; B) failure to list the correct animal source in the final report; C) one animal observation was mis-recorded; and D) dried residue was found on supposedly clean guinea pig cages. Jon C. Fulfs, Ph.D., who signed the reports of both 128.001 and 128.002 as the study director, stated that Atrix used the facilities of but had their own personnel conduct the study and retained all records. Mr. Hein's review recommended an inspection of Atrix Laboratories. I contacted OSI and requested an update of the situation; the response was pending at the time my review was completed. The data submitted under study No. 128.002 should be interpreted with reservation.

Six adult female Beagle dogs were selected for treatment with both a 5% (lot No. JAR-57-55-5) and a 10% formulation (lot No. JAR-57-55-10) of doxycycline hyclate in vehicles that consisted of PLA and NMP (the same formulations listed in section 3.1.5, above). The formulation proposed for marketing (8.5% doxycycline in a base consisting of 36.7% PLA and 63.3% NMP) was not tested in this study. Naturally occurring periodontal pockets were selected in each dog; after the test sites were cleaned, each pocket was either filled with one of the gels or flushed with saline. The amounts of test material deposited per site varied from mg in animals that received 5% gel and from mg in animals that received 10% gel. The animals were observed daily until sacrifice. The test sites were observed grossly for erythema, edema (both assessed according to a standardized Draize technique on a scale of 0 to 4), and other

signs of irritation at 3, 6, 12, and 24 hrs. post-treatment, and daily thereafter until the dogs were killed on day 28. Samples of GCF were collected at 3, 6, 12, and 24 hrs., and then daily until termination. Blood samples were collected at 6, 12, 24 hrs., and on days 2, 3, 4, 5, 6, 7, 10, 14, 21, and 28. The GCF and blood were analyzed for doxycycline concentration. Histopathology was not performed.

Results.

Clinical signs. No mortality or abnormal behavior was reported. All animals gained weight in a normal manner.

Macroscopic pathology. Slight erythema and edema were initially observed but had both essentially returned to baseline by the third day post-treatment. The erythema and edema that were observed may have been secondary to the cleaning procedure, although the data suggest a trend toward a dose-relatedness of the effects during the first 12 hours after treatment.

Retention of the test material. The numbers of sites with observable test material at each time point diminished slowly during the 28 day observation period; approximately one-third of the sites still contained the test material on day 28. However, the product is only intended to be retained for approximately 7 days, and 8 of 9 sites that received the 5% formulation and 7 of 9 sites that received the 10% formulation contained the test material on day 7.

Concentration of doxycycline in the GCF. The change in doxycycline concentration in the gingival crevicular fluid over time is presented on the following page.

Mean Concentration of Doxycycline in the GCF (Mean±SD)

Time (hours)	Vehicle Control —	5% Formulation	10% Formulation
3	55±56	1776±947	1592±930
6	33±47	1390±1327	1749±5646
12	29±25	1291±1423	1303±1242
24	31±24	945±662	1077±1064
48	15±23	724±816	534±436
72	10±24	364±306	265±176
96	0±0	260±342	310±322
120	0±0	154±193	539±640
144	0±0	118±94	367±321
168	0±0	259±329	457±703
240	0±0	261±351	126±96
336	0±0	32±29	114±172
504	0±0	157±323	99±92
672	0±0	133±156	48±10

Limit of Detection = 0.1µg/mL

Concentration of doxycycline in the serum. Doxycycline was detected in the serum of only one dog at a value above the limit of quantitation µg/mL; the measured value was µg/mL, obtained 6 hours after treatment), although values above the limit of detection (µg/mL) were observed in several dogs at 6 and 12 hours after treatment. All levels were below the limit of detection by 24 hours after treatment.

Conclusion. These data suggest that the test products were not substantially irritating under the conditions of the study. Only minor erythema and edema were observed, and these effects returned to baseline by the third day post-treatment. Doxycycline was present in the GCF at measurable concentrations throughout the study. Under the conditions of this study, detectable serum levels of doxycycline were observed in some of the dogs during the first 12 hours post-treatment.

3.1.7. Subcutaneous irritation study in rabbits, study No. 558-018, Atrix study No. ATS-19, in-life 6/88, conducted by in compliance with Good Laboratory Practice regulations (21 CFR 58).

This study was performed to assess the cytoxicity of the inactive ingredients of Atridox®; the cytoxic potentials of: 1) pure PLA; 2) a 1:1 mixture of PLA and NMP; and 3) USP Negative Control Plastic were compared following subcutaneous placement on the backs of nine rabbits. Two test sites per test article were used on each rabbit, one on either side of the spine. The USP negative control plastic and the PLA polymer were surgically introduced through incisions at a dosage level of 50mg; the PLA/NMP mixture was introduced via subcutaneous injection at a dosage level of 0.1 mL (120mg). The negative control plastic was cut into small segments and autoclaved prior to placement in the test sites. The test sites were evaluated for signs of local irritation immediately after administration, 1 hour post-administration, again 3 to 6 hours post-administration, and once daily thereafter until the animals were euthanized at either 7, 14, or 21 days.

Results. Very slight erythema and/or edema was evident in most rabbits on days 2 and/or 3 and persisted in some of the rabbits until their scheduled termination. Sporadic incidences of a slightly greater degree of irritation were observed in rabbits injected with test article that contained NMP. Macroscopic responses to the PLA alone and to the PLA/NMP mixture were similar to the response to the negative control (USP Negative Control Plastic). The responses were moderate and were characterized by induration, red discoloration and hemorrhage. Macroscopically, there was no meaningful difference between these groups at 7 or 21 days. Implant sites for the PLA and PLA/NMP were similar to the control sites with respect to irritancy. At 7 days, occasional minimal necrosis was noted which was judged to be attributable to the implantation procedure.

Conclusions. The irritation potential of the negative control, the PLA, and the PLA/NMA were considered to be similar and all adverse effects that were observed resolved over time. These data suggest that the excipients in Atridox® are not cytotoxic, and would not be expected to induce necrosis or other adverse effects at the treatment site.

3.1.8. Gingival irritation study in dogs, study No. 558-019, Atrix study No. ATS-20, in-life 6/88, conducted by , in compliance with Good Laboratory Practice regulations (21 CFR 58).

This study was performed to assess the potential of a 1:1 mixture of PLA and NMP to cause erythema or edema in 10 dogs following placement within subgingival pockets that had been created by tooth extraction. The test material (0.1mL) was

placed within a pocket and sutured in place for 4 to 7 days. Saline (0.9%) was used as a control material. The treated sites were examined 4 hours after placement and daily thereafter. The animals were sacrificed either 15 or 22 days following treatment and histopathology of the gingiva surrounding the treatment site was performed.

Results. Four dogs exhibited slight gingival irritation at each test site, including the control site, on study days 3 and 4. This condition resolved by day 5. Three other dogs exhibited slight irritation at one or more test sites (including the control site) on study days 7, 8, or 9. Emesis was noted at approximately 2 1/2 hours post-administration on day 1 in one dog, but was resolved by hour 4. This finding was considered to be related to the trauma from the surgical procedure and not related to test article administration. No other macroscopic signs were noted in any other dog. No remarkable changes or differences were noted in body weight during the study. Histologically, sites that received the test material exhibited slightly more inflammation at the time of sacrifice than did control sites.

Conclusions. These data suggest that the vehicle of Atridox® is minimally irritating when in contact with the gingiva.

3.1.9. Primary dermal irritation following subcutaneous injection in rabbits, study No. 129.012, ATS-47, in-life 10/91, conducted at
in compliance with Good Laboratory Practice regulations (21 CFR 58).

This study was performed to assess the potentials of the test articles to induce primary irritation following subcutaneous injection. The test articles studied included NMP, gamma-irradiated NMP (Mega-rad), Atridox® vehicle % PLA/ % NMP polymer), gamma-irradiated Atridox® vehicle, and gamma irradiated % PLA/ % NMP polymer. Eighteen rabbits were divided into three groups to collect irritation potential data from three different time points: Group I (6 rabbits) - 7 days; Group II (6 rabbits) - 14 days; and Group III (6 rabbits) - 21 days. All test sites were observed at 1 hour, 6 hours, and on Days 1, 4, and 7 following test article administration. Test sites on the remaining rabbits were observed on Days 14 and 21, respectively, and graded for erythema and edema on a scale from 0 to 4. All animals were observed daily for overt signs of toxicity.

Results. No erythema or edema was observed at any of the test sites during the course of the study. None of the animals exhibited any signs of overt toxicity during the course of the study. Small areas of redness and small scabs were observed around the injection sites. Small areas of red petechiae were

observed subcutaneously in the same areas at necropsy. These appeared to be related to the mechanical injection procedure and not to the test articles. The pathology report indicated that no particular response could be associated with any specific test article.

Conclusions. The test articles in this study, including the vehicle of Atridox®, were not irritating to the skin when placed subcutaneously for 21 days and evaluated both macroscopically and histologically.

3.1.10. Subchronic subcutaneous polymer implantation study in rabbits, study No. 129.002, ATS-36, in-life 5/90-8/90, conducted at in compliance with Good Laboratory Practice regulations (21 CFR 58).

This study was performed to determine the rate of degradation of the test materials, *in vivo*, and to assess the potentials of the test articles to induce a dermal response following subcutaneous injection. The test articles studied included % PLA/ % NMP formulations (Atrigel) of several viscosities, with and without % polyvinyl pyrrolidone (PVP), which was added to make the polymer formulation more porous. Each of the test articles were placed subcutaneously in the backs of one male and one female rabbit per test article group to determine the local tissue response potential of each test article. Four separate test sites, representing four implantation dates, were used on each rabbit. The test articles were administered via syringe fitted with a 23 gauge blunt cannula to site one on day 0, to site two on day 28, to site three on day 56, and to site four on day 70. Animals were euthanized on day 84, and the test sites were removed for histopathology. Thus, data generated represent the tissue response for each test article at 14 days, and at 1, 2, and 3 months. All animals were observed daily for overt signs of toxicity. All surgical sites were examined daily unless bandages were in place.

Results. Five animals died during the course of the study. The death of three animals within the first few days following surgery was attributed to hypotension due to anesthesia. One animal was found dead on Day 50. The fifth animal died on Day 82. At necropsy, the stomach and intestines were gas filled and there was evidence of diarrhea in the large intestine. None of the deaths was considered to be related to the test article. Observations of the surgical sites revealed some redness, edema, hair loss, skin sensitivity, and exudate. Generally, these observations were made within the first 10 days following implantation, and all but six of the 96 sites had completely healed by study completion. The unhealed sites exhibited redness

and swelling at the time of necropsy. An exudate was also noted at two of the unhealed sites (both in the same animal). Histopathology revealed minimal muscle loss immediately below the dermis, as well as the presence of some fibrous tissue in the same area. Cyst formation was restricted to the area immediately surrounding the polymer and seemed to resolve over time.

Conclusions. Tissue response to the test articles appeared to be limited to a normal physiological response to the presence of a polymer mass and/or to the surgical procedure itself.

3.1.11. 12 month subcutaneous implantation test in rabbits (surgical method) with histopathology, ATS-63, in-life 10/93-10/94, conducted by in compliance with Good Laboratory Practice regulations (21 CFR 58).

This study was performed to determine the potential of "Atrisorb® Barrier-100 membrane prepared with a Barrier forming kit" to cause a toxic response when surgically implanted into subcutaneous tissue. The test material was composed of % PLA and % NMP, apparently materials identical to the excipients in Atridox®, and was in a sheet 10mm x 10mm and approximately µm thick. Each of 52 rabbits had the test material (4 sites) and USP plastic controls (2 sites) surgically implanted. The test sites were rotated on each animal to determine any potential for site specificity. Animals were then euthanized in groups of 4 every 28 days for 12 months. Daily manual assessments of tissue response were made up to day 18. Following termination, subcutaneous tissues were excised and the implant sites examined macroscopically and histologically.

Results. Two groups showed slight body weight loss from day 0 to day 14. This was attributed to the trauma of the implantation procedure and was not considered to be related to the implanted test material. All other body weight changes were considered to be within normal limits. There was slight edema above both the test and control sites until 18 days after surgery. No erythema was noted above the implanted materials in any of the groups during this period. There were no dermal reactions noted in any of the animals after day 18 that were attributed to the implanted materials. Macroscopically, a white encapsulation was noted in a few animals at various time points following termination. This encapsulation was observed around two implanted polymer formulations and two implanted controls at month 4. The same type of encapsulation was noted in two polymer formulation sites and one control site at month 6. At month 7, encapsulation was observed around a total of seven polymer formulation sites and four control sites. Six polymer formulation sites and four control sites at month 8 also showed evidence of encapsulation. In addition, small areas of tissue reaction were noted around the implanted material at months 10 and 11. A gross visceral necropsy was performed on all animals exhibiting encapsulation,

with no other macroscopic changes noted. The microscopic evaluation showed a minimal to mild fibrous response delineating most of the control and test implant sites with some associated histiocytic inflammation. Both the histiocytic and fibrotic reaction delineating these implant sites was considered to be biologically insignificant. Histiocytes and multinucleated cells typically form around material which is physically irritating and is more a function of the structure of the implanted material than due to any inherent chemical toxicity of the test material. The results of the microscopic evaluation showed no significant differences between the test and control materials in any of the twelve groups.

Conclusion. Under the conditions of this study, no significant differences were observed between the implanted test and control materials with respect to tissue compatibility.

3.2 Repeat-Dose and Chronic Toxicology. The proposed label for Atridox® would limit use of the product to a single administration (containing 100mg or less of doxycycline), to be repeated at four month intervals. Repeat-dose and chronic toxicology studies are not necessary to support marketing of Atridox®, particularly in view of the clinical experience with doxycycline hyclate (Vibramycin® is currently labeled for daily administration of 100mg of doxycycline hyclate per day for up to 4 months for prophylaxis against malaria).

3.3 Specialty Toxicology.

3.3.1. Dermal sensitization study in the albino guinea pig (Buehler), study No. 558-026, ATS-28, in-life 10/89, conducted by in compliance with Good Laboratory Practice regulations (21 CFR 58).

Note: The test articles used in this study varied slightly from the formulation that is proposed for marketing, but were sufficiently similar that the data are (in my opinion) relevant to the to-be-marketed formulation.

Groups of young adult Hartley guinea pigs were randomized to receive either saline (control group; 5 males and 5 females) or one of 3 formulations of doxycycline hyclate (5, 10, or 20%; 10 males and 10 females in each group) in a gel base consisting of PLA and NMP. The formulations of the 5% and 10% test products were the same as given in section 3.1.5, above; the formulation of the 20% product is not stated but was apparently similar to the 5% and 10% products. The "induction" phase of the study involved application of 0.4ml of the appropriate test gel to shaved regions of guinea pig skin; the sites were covered with an adhesive patch which was occluded with rubber. The patch and test material were removed 6 hours after application. The induction procedure was repeated at the same sites twice at 7 day intervals. Control animals underwent a similar procedure in which saline was applied. All animals were "challenged" 28 days after the initial application through an additional application of the appropriate test material in the same manner as during the induction phase; control animals were challenged at 4 sites, including a site that received saline and 3 sites that each received one of the test gels. The application sites were examined 24, 48, and 72 hours after the final application.

Results. The test animals and the control animals did not differ in terms of observed erythema.

Conclusion. The test products were considered to be non-sensitizing under the conditions of this study.

3.4 Reproductive Toxicology.

3.4.1 Fertility/reproductive success. A fertility study was waived, partially because of the extensive clinical experience that exists with doxycycline at higher-levels of exposure and partially in view of the short duration of exposure to doxycycline that would result from use of the product (approximately 7 days).

3.4.2 Teratology/fetal toxicity. Teratology studies were waived because pregnancy category "D" class-labeling is associated with tetracyclines.

3.4.3 Developmental toxicity (peri/post-natal assessment). Developmental toxicity studies were waived, partially because of the extensive clinical experience that exists with doxycycline and partially because tetracyclines carry class-labeling against use during the last half of pregnancy, infancy, and childhood to age 8 due to tooth discoloration.

3.5 Genetic Toxicology. Doxycycline was not evaluated for genetic toxicity under NDA 50-751; the sponsor was promised years ago that genetic toxicology studies would not be required to support marketing of Atridox® in view of the fact that higher levels of exposure to doxycycline over longer periods of time than proposed in regard to Atridox® have long been deemed to be "safe", even for relatively trivial indications (although such studies would be expected under today's standards).

3.6 Carcinogenicity. Doxycycline has not been assessed for potential to induce carcinogenicity. However, Atridox® is not indicated for chronic use, and therefore NDA 50-751 does not require support from such assessment. It should be noted that evidence exists that some related antibiotics are carcinogenic in rats; oxytetracycline induced adrenal and pituitary tumors, while minocycline caused thyroid tumors.

3.7 Toxicology of N-methyl-2-pyrrolidone (NMP). The submission included some published articles that concerned the toxicology of NMP (an inactive ingredient of Atridox®). This material is briefly discussed below:

- Oral LD_{50} estimates: mouse, 4.0g/kg; rat, 4.2g/kg; guinea pig, 4.4g/kg; rabbit, 3.5g/kg.
- Rabbits that received five 0.4mL/kg oral doses of NMP per week for 25 doses apparently exhibited no pathology; end points examined included "blood, liver and kidney function, and histopathology".
- "Rats administered 2.5, 0.25, and 0.025mg/kg [by mouth] for 6 months showed an increase in reticulocytes, neutrophils, and liver glycogen content...The no effect level was considered to be 0.25mg/kg[/day]. Rabbits receiving the identical dose regimen failed to show effects".
- Wistar rats (25/sex/group) received NMP at concentrations of 0, 800, 2000, and 5000ppm in the diet for 90 days (estimated exposures of 0, 40, 100, and 250mg/kg/day for females and 0, 40, 100, and 300mg/kg/day for males). Parameters monitored included weight gain, clinical signs, clinical chemistry, and gross and histopathologic examination. The only effects that were considered to be treatment-related (apparently seen in high-dose males only) were increased thyroid weights and elevated SGPT. The 2000ppm exposure level (approximately 100mg/kg/day) was considered to be a NOAEL. Similar data were apparently obtained in a 90 day dietary study in mice, except that the NOAELs were estimated at 48mg/kg/day in males and 120mg/kg/day in females.
- In a 90 day dietary study in Beagle dogs, a NOAEL of 250mg/kg/day was estimated.
- NMP apparently yielded negative results in the Ames test, the mouse lymphoma L5178Y cell line, the CHO/HGPRT assay, and in a UDS assay in primary rat hepatocytes.
- In a study in which male rats received radiolabeled NMP by IV injection, the plasma half-life was estimated at 8hrs.; the compound was primarily excreted in the urine, with 70% of the dose accounted for within 12hrs. The urine contained several metabolites of NMP.

Summary:

Pharmacodynamics. Doxycycline hyclate is an antibiotic compound with activity against many species of bacteria when administered at sufficient dosage. Please see the approved label for NDA 50-006 (Vibramycin) for a list of the species against which doxycycline has been proven to be effective. Presumably, antimicrobial activity accounts for the action of Atridox in the treatment of periodontitis.

ADME, Pharmacokinetics. Following placement of a test material similar to Atridox® (10% doxycycline in Atrigel) within periodontal pockets of dogs, a T_{max} for doxycycline within the GCF of 6 hours was observed. The concentration of doxycycline in the GCF gradually declined, approaching zero after approximately 10 days. Doxycycline was detected in the serum of only one dog at a value above the limit of quantitation (0.4µg/mL), and that was at 6 hours after treatment, although values above the limit of detection (0.1µg/mL) were observed in several dogs at 6 and 12 hours after treatment. All levels were below the limit of detection by 24 hours after treatment.

Doxycycline is generally well absorbed from the GI tract, although aluminum-containing antacids will interfere with absorption. Apparently, the extent of protein binding is variable, ranging from % . Published values for the serum half-life and renal clearance of doxycycline are 14.5-22 hours and 16ml/min., respectively. The primary route of elimination of doxycycline is excretion in the bile; elimination of doxycycline is apparently not compromised by renal dysfunction.

Single-Dose toxicology. Studies in which either Atridox® or the vehicle in Atridox® was administered on a single occasion into either a periodontal pocket of a dog or into the subcutis of a rabbit demonstrated that the test materials did not cause excessive toxicity (including local irritation or inflammation).

Repeat-Dose and Chronic Toxicology. The proposed label for Atridox® would limit use of the product to a single administration (containing 100mg or less of doxycycline), to be repeated at four month intervals. Repeat-dose and chronic toxicology studies are not necessary to support marketing of Atridox®, particularly in view of the clinical experience with doxycycline hyclate (Vibramycin® is currently labeled for daily administration of 100mg of doxycycline hyclate per day for up to 4 months for prophylaxis against malaria).

Reproductive Toxicology:

Fertility/reproductive success. A fertility study was waived,

partially because of the extensive clinical experience that exists with doxycycline at higher-levels of exposure and partially in view of the short duration of exposure to doxycycline that would result from use of the product (approximately 7 days).

Teratology/fetal toxicity. Teratology studies were waived because pregnancy category "D" class-labeling is associated with tetracyclines.

Developmental toxicity (peri/post-natal assessment). Developmental toxicity studies were waived, partially because of the extensive clinical experience that exists with doxycycline, and partially because tetracyclines carry class-labeling against use during the last half of pregnancy, infancy, and childhood to age 8 due to tooth discoloration.

Genetic Toxicology. Doxycycline was not evaluated for genetic toxicity under NDA 50-751; the sponsor was promised years ago that genetic toxicology studies would not be required to support marketing of Atridox® in view of the fact that higher levels of exposure to doxycycline over longer periods of time than proposed in regard to Atridox® have long been deemed to be "safe", even for relatively trivial indications.

Carcinogenicity. Doxycycline has not been assessed for potential to induce carcinogenicity. However, Atridox® is not indicated for chronic use, and therefore NDA 50-751 does not require support from such assessment.

Labeling: The following modifications of the draft labeling of NDA 50-751 are recommended:

1. Carcinogenesis, Mutagenesis, Impairment of Fertility. Please change this section to read:

2. Pregnancy Category. Please change this section to read:

Evaluation: Please see page 22 of this document for a summary of the pharmacodynamics and toxicology of Atridox®. Although Atridox® may be used more than once in a given individual (at four month intervals), use of the product would entail very low-level exposure to the drug substance for only 7 to 10 days per treatment episode, with an estimated lifetime exposure to doxycycline as a result of use of Atridox® of 21 to 30 days. The product is not indicated for chronic use. Studies in which either Atridox® or the vehicle in Atridox® was administered on a single occasion into either a periodontal pocket of a dog or into the subcutis of a rabbit demonstrated that the test materials did not cause excessive toxicity (including local irritation or inflammation). In view of the database accumulated during 30 years of human use of doxycycline and the low level of exposure proposed (2mg/kg/dose or less of doxycycline in a 50kg individual, followed by a 4 month wash-out period), the existing nonclinical data are adequate to support the safety of NDA 50-751.

Recommendations: NDA 50-751 is approvable in regard to pharmacologic and toxicologic concerns. Recommended changes in the product label are indicated above.

9/24/97

/S/

Norman A. See, Ph.D., R.Ph.
Reviewing Pharmacologist

cc:
NDA 50-751
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