FREEDOM OF INFORMATION SUMMARY

1. General Information

New animal drug application number: D 136-383

Sponsor: Luitpold Pharmaceuticals, Inc.
5 Ramsay Road
Shirley, New York 11967

Generic name of drug: Polysulfated Glycosaminoglycan

Trade name: Adequan

2. Product indications

Adequan is recommended for the treatment of non-infectious degenerative and/or traumatic joint dysfunction and associated lameness of the carpal joint in horses.

3. Dosage and Administration

The recommended dose of Adequan in horses is 250 mg (1 ampule) once a week for five weeks, intra-articularly. The joint area must be shaven, cleansed and sterilized as in a surgical procedure prior to injection. Do not mix Adequan with other drugs or solvents.

4. Effectiveness

Adequan for the treatment of lameness in horses has been evaluated in both a dose titration study and in field trials. There were 30 horses studied in the dose titration investigation and 109 horses in the field trials. All of these trials are pivotal.

Dose Titration Investigation

The Dose Titration investigation was performed by Drs. Doyne Hamm and Gary White of Fayettville, Ak. 72701. Dr. Wynn E. Jones of Missisippi State University served as the quality control director of this study. This study was conducted on a double blind basis, i.e. the veterinarian who administered the drug did not know what the dosage was and the quality control director who evaluated the response to the drug, did not know which treatment each animal received.

An induced adjuvant carpitis in the horse was used to assess the dose and efficacy of the intraarticular administration of Adequan. The model used produces:

1. A syndrome which is pathologically and temporarily compatible with the use of Adequan
2. A sufficiently uniform syndrome which permits practical group sizes for statistical analysis
3. Response parameters (joint circumference, stride length, joint position at rest, etc.) which permit quantitative assessment of any response
4. Characteristics which provide for confirmation of the syndrome (eg. joint fluid and necropsy parameters).

Healthy, mature animals of quarter horse or thoroughbred type served as experimental animals. These animals were acclimated to the enviornment, maintained in covered stalls and were fed a routine weight maintenance ration with hay and water ad libitum.

The adjuvant induced arthritis was produced with a single intraarticular injection of 0.5 ml of Freunds Adjuvant using standard aseptic techniques and precautions. This model is characterized by inflammatory exudation into the joint cavity, inflammation of the synovial membrane, periarthritis, lipping and osteitis.

The various treatments comprised sterile saline solution as a placebo control, 5.0 mg, 125 mg, 250 mg, and 500 mg of the active drug substance in Adequan dissolved in sterile water. Injections were given once a week for five weeks. Treatment followed a 10 day acclimation period, and a five day model induction period. The study was conducted in replicates of five in which all treatment groups were represented.

Observations consisted of the following:

1. clinical - temperature, pulse & respiration
2. lameness (once weekly) prior to treatment
   a) angle of flexion prior to treatment
   b) maximum angle of flexion permitted
   c) length of stride (lame limb)
3. limb circumference
4. joint fluid - total protein at time of treatment
5. radiograph - initial and at study conclusion
6. hemogram - cell blood count/hematocrit, once weekly
7. necropsy - gross and histological observations

A statistical analysis (analysis of varience) was performed to test for dose effect. There were no statistical differences that were considered significant in any of the measurements except for those related to lameness. These parameters are flexion after rest, maximum flexion permitted, stride lengths after rest and exercise, limb circumference and synovial fluid protein levels. Table 1 indicates the changes in these parameters for the dosage of 250 mg. Statistically this dosage is the same as the 500 mg dosage. The other dosages (placebo, 5 mg and 125 mg) can be considered as statistically different from the 250 mg and 500 mg groups but the same as each other. The significance of all variables given in Table 1 is .0001. This is considered highly meaningful. The smaller the number, the higher the significance.

	Flex Rst	Flex Max	Std Rst	Std Exr	Cir	Protein
Before Model Induction	180	148	61.9	62.4	11.38	1.7
Induction + 5 Days	177	72	53.9	52.0	13.13	4.9
1 Week After 5th Injection	180	143	60.9	61.5	11.79	1.9

Table 1 : Lameness related variables from dose titration study. All measurements from the 250 mg dose group.

Flex Rst = Flexion after rest measured in degrees
Flex Max = Maximum flexion permitted in degrees
Std Rst = Stride length after rest in inches
Std Exr = Stride length after standardized exercise, inches
Cir = Circumference of affected joint in centimeters
Protein = Synovial fluid protein level in mg/ml

All values are the averages of 6 measurements, taken at the same intervals for all animals in this treatment group.

An examination of this table indicates that the values before model induction were rather severly changed because of the model induction. For each of these parameters these changes were indicative of lameness. Examination of the third horizontal column (After 5th Injection) indicates that 250 mg of the active ingredient in Adequan (PSGAG) returns the joint to almost the normal, pre- model induction condition.

	Flex Rst	Flex Max	Std Rst	Std Exr	Cir	Protein
Before Model Induction	180	147.5	62.5	63	11.63	2.0
Induction + 5 Days	180	75	52.8	50.9	13.74	5.3
1 Week After 5th Injection	180	145	61.3	61.7	11.9	2.0

Table 2 : Lameness related variables from dose titration study. All measurements from the 500 mg dose group.

Flex Rst = Flexion after rest measured in degrees
Flex Max = Maximum flexion permitted in degrees
Std Rst = Stride length after rest in inches
Std Exr = Stride length after standardized exercise, inches
Cir = Circumference of affected joint in centimeters
Protein = Synovial fluid protein level in mg/ml

All values are the averages of 6 measurements, taken at the same intervals for all animals in this treatment group.

An examination of this table indicates that the values before model induction were rather severly changed because of the model induction as in the previous Table 1. Examination of the third horizontal column (After the 5th Injection) indicates that 500 mg of PSGAG has the same beneficial effect as the 250 mg dose group. Statistically the 500 mg dose group is the same as the 250 mg dosage group.

	Flex Rst	Flex Max	Std Rst	Std Exr	Cir	Protein
Before Model Induction	180	147	65.1	61.7	11.4	1.8
Induction + 5 Days	173	65	54.3	53.4	13.67	5.0
1 Week After 5th Injection	180	67	57.7	56.8	14.17	4.0

Table 3 : Lameness related variables from dose titration study. All measurements from the 125 mg dose group.

All values are the averages of 6 measurements, taken at the same intervals for all animals in this treatment group.

An examination of Table 3 shows the same effect of model induction, ie. changes from normal values to indicators of severe inflammation and joint involvement. Examination of the third horizontal column (After 5th Injection) indicates that 125 mg of PSGAG does not have as much of a beneficial effect as the 250 mg dose group. Although the 125 mg group showed more improvement than lower dosages statistically the placebo and 5.0 mg groups are the same as the 125 mg group.

At the conclusion of this study, gross and histologic observations of the affected carpus joint were made on selected animals from each treatment group by Dr. J.N. Beasley. Dr. Beasley is a veterinary pathologist at the University of Arkansas at Fayetteville, Ak. 72701. He concludes that there were no remarkable changes in the bone and cartilage of the subject animals upon gross examination. Joint surfaces were smooth and glistening. Histologic examination revealed nothing remarkable in bone and cartilage samples. Other findings were not significant.

The conclusion that can be drawn from this dose titration study is that for the parameters associated with lameness ie. flexion, stride length, joint circumference and synovial fluid protein levels,250 mg of Adequan is the optimal dosage. The possibility that this finding is a product of chance is less than one in ten thousand. At this dosage one would not expect to find any harmfull effects on the bone or cartilage or systemically.

Field Trials

A waiver from the requirement for comparison between Adequan and an approved, marketed product which treats the same symptoms was granted by F.D.A. on 7 March, 1983. This waiver was based on the fact that no such marketed product has been approved in the U.S. A copy of this waiver is attached.

Eight field trials were conducted to demonstrate that Adequan, when used under field conditions, had the same beneficial characteristics as were shown during the dose titration study. The participating veterinarians were chosen so as to provide good geographical distribution across the U.S. Each of these veterinarians is suitably qualified to investigate the effectiveness of drugs used to treat lameness in horses, by virtue of their training and experience.* A total of 109 horses were treated with Adequan in the field trials. An animal had to demonstrate either elevated synovial fluid protein levels or decreased viscosity. Synovial fluid analysis is an accepted method for the determination of joint dysfunction in horses.

* A listing of participating veterinarians follows.

204 INAD 2515
Glycosaminoglycan Polysulfuric Ester
(L-1016)
Lawrence Goldman, Agent
Luitpold-Werk
Munich, Germany
February 23, 1983

WAIVER FROM THE REQUIREMENTS OF 21 CFR 514.111(a)

Subject: INAD 2515 (Fast Track)

L-1016 (mucopolysaccharide polysulfuric ester) is indicated to prevent or reduce chronic arthrotic type degenerative joint changes in the horse without impairment of regenerative response.

In accordance with provisos of Section 514.111(a)(5)(vi), a waiver of criteria defining adequate and well-controlled investigations in Section 514.111(a)(5) is being granted with respect to controlled field studies in horses. This request is being granted based upon the following facts which permit the conclusion that controlled clinical studies are not possible and will not add significantly to our knowledge of the efficacy of the article for the reference use.

1. Dose-response studies indicate that weekly intra-articular injection of L-1016 (glycosaminoglycan polysulfuric ester) into the equine carpus for up to six weeks have been found to be effective for the improvement of joint function. Currently there is no approved drug which could be used for long term therapy for a positive control for the referenced indications in the horse.

2. In the population of animals for which the drug is intended and will find its most use, it is not possible to use a negative control. This drug's greatest potential for use is with the young (2-4 years), valuable competitive event horses whose future potential mandates that they will be exposed to some type of empirical treatment which would not provide appropriate comparison with L-1016.

3. The course of this disease, chronic arthrotic type degenerative joint changes, is unpredictable and precludes the animal from serving as its own control.

Lester M. Crawford, DVM, PhD
Director
Bureau of Veterinary Medicine

cc: Orig., HFV-16
Dr. Crawford, HFV-1
HFV-112

F.O.I. SUMMARY continued

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Dr. W. Tew is responsible for the analyses in this study. He is president of Equine Diagnostics Laboratories, P.O.Box 4583, Baltimore, Md. 21212.

Elevated synovial fluid protein levels are indicative of synovial effusion. This is a condition related to an active inflammatory process and is often associated with joint lameness. Decreased synovial fluid viscosity levels are indicative of synovial membrane dysfunction. This means that the fluid within the joint which should be a good lubricant has lost a portion of its ability to facilitate the movement of one joint surface over the other.

Injections of Adequan were given in 250 mg doses weekly for up to five weeks to horses with either elevated synovial fluid protein levels or lowered viscosity levels. Horses with carpitis were selected on the basis of clinical judgement as well. Pain, degree of carpal flexion, swelling,heat and lameness were evaluated clinically at the start of treatment and at weekly intervals. Pain was determined on basis of presence or absence on palpation; degree of carpal flexion was determined as 30,60,90 or more than 90 degrees with a protractor; swelling of the affected joint, at the most swollen place, was graded by the investigator on a scale of 0,1,2,or 3; heat at the affected joint was determined by the investigator as present or absent to the touch; lameness was graded on a 0,1,2,or 3 scale by the investigator. The scale for lameness and swelling are 0 = normal; 1 = mild; 2 = moderate and 3 = severe. Improvement is defined as a change from a higher value to a lower one. (see Table 4).

The 109 horses ranged in age from 2 to 15 years, the majority being 3-year-olds. There were 25 males , 40 females and 44 geldings as subjects.More than half (61%) of the horses had shown signs of lameness for at least four weeks. The amount and quality of exercise given to these animals varied greatly: 23 were heavily exercised and 39 were being rested or receiving only light exercise; no specific information was available for the remainder. About 25% of the horses were reported to have carpal chips.

By means of initial clinical observations, 93% were found to be lame, 73% had pain on palpation, 86% had pain on carpal flexion, 74% had impaired flexion, 87% had carpal swelling, and 92% had detectable heat at the site of the lesion.

Intercarpal injections of 250 mg ADEQUAN were administered weekly for up to five weeks. Determination of efficacy was contingent upon improvement of clinical and joint fluid parameters.

Responses to treatment were plotted over time. As expected, not all of the animals remained in the study until it was completed. 70 animals received the full treatment. This may reflect the fact that those remining under treatment for all five injections were more seriously afflicted. They were more likely to have had only limited exercise, a bone chip, and a longer history of clinical signs. Animals that responded early were more likely to have been withdrawn from the study. 7 of the 109 animals (6.4%) received only 2 injections and were evaluated as excellent or good responders to treatment.

Based on the clinical variables studied, improvement was apparent by the time of the second injection. These findings were comparable to the observations made in the study of experimentally induced carpitis. Heat due to inflammation disappeared most rapidly, followed by pain on palpation and flexion, then lameness, reduction in swelling, and finally increase in the degree of carpal flexion.

Comparison of the initial values for protein in joint fluid of 85 animals for which data were available versus their final values indicated improvement in 72% of the animals. Changes in viscosity of joint fluid were present but less apparent.These values were influenced by early withdrawal of horses from the study and by the presence of carpal chips. Improved viscosity was significantly less likely to be gained in animals withdrawn early from the study and in animals having carpal chips. The mean percentage change in viscosity was a reduction of 20% for horses withdrawn early from the study and an increase of 24% for horses receiving all five injections.

When the participating veterinarians rated the clinical responses of the 109 horses, 2 (1.8%) were judged to have a poor response, 8 (7.3%) a fair response, 45 (41%) a good response, and 54 (49.5%) an excellent response.

The only side effect observed after injection, was transient lameness (less than four hours) in 2 animals (1.8%).

An examination of Table 4 will indicate the changes in clinical variables related to treatment.

Variable	Number Horses Improved	Number Horses not Improved	Number of Horses Data Incomplete
Lameness	90	2	17
Pain on Palpation	71	0	38
Pain on Flexion	74	0	35
Degree of Flexion	54	3	52
Swelling	77	0	32
Heat	75	0	34

Table 4 Changes in Clinical Variables Related to Treatment. Improvement is defined as a decrease in the degree of the listed variables.

5. Safety

Adequan, for the treatment of non-infectious degenerative and/or traumatic joint dysfunction and associated lameness of the carpal joint,has been evaluated in a dose response study, 8 field trials, a sub-acute toxicity study and 10 preclinical investigations. Hazelton Laboratories of Vienna,Va. 22180,conducted these pre-clinical investigations. A listing of these studies follows:

1. Acute Intravenous Toxicity Study in Rats
2. Thirteen Week Toxicity Study in Rats
3. Acute Intravenous Toxicity Study in Dogs
4. Thirteen Week Intra-Articular Toxicity Study in Dogs
5. Fertility Study in Female Rats
6. Teratogenicity Study in Rabbits
7. Salmonella Typhimurium Mammalian Microsome Plate Incorporation Assay
8. L5178Y Mouse Lymphoma Forward Mutation Assay
9. In-Vivo Cytogenetic Assay in Rats
10. Fertility Study in Male Rats

Summaries of these studies are attached. There was no meaningful evidence from these studies that indicated that the active ingredient in Adequan (PSGAG) would be toxic.

Synopsis of G.A.G.P.S. (Mucopolysaccharide Polysulfate) Preclinical Investigations

Project No. 2144-100 : Acute Intravenous Toxicity Study in Rats

The acute intravenous LD50 in male rats was calculated to be 2,077 mg/kg of body weight and in female rats to be 4,576 mg/kg of body weight. The combined LD50 in males and females was calculated to be 3,848 mg/kg of body weight.

Project No. 2144-101 : Thirteen-Week Toxicity Study in Rats

The subchronic toxicity following daily administration by intra-muscular injection for four or thirteen weeks in male and female rats at dose levels of 2, 10 and 25 mg/kg of body weight was determined. One high-dose female died at Week thirteen. Survival was comparable among all treated and control groups. Growth rates, food consumption and mean body weights were generally comparable among all groups. Hematology, clinical chemistry and urinalysis from Weeks four and thirteen were unremarkable for all groups. Statistical evaluation of mean organ weights at Week thirteen revealed several significant differences between control and treated groups. At Week thirteen, myositis, hemorrhage and resolving hematocysts were observed in muscles from high-dose males and females. This finding suggests that G.A.G.P.S. is more irritating than control on injection. Histiocytosis was observed in mesenteric lymph nodes from high-dose males and females sacrificed at Week thirteen. No neoplastic lesions were observed in any animals any time.

Project No. 2144-102 : Acute Intravenous Toxicity Study in Beagle Dogs

The acute intravenous toxicity of G.A.G.P.S. in male and female beagle dogs was evaluated at dose levels of 0.25, 0.50, 1.0, and 2.0 g/kg of body weight. The 2.0 g/kg male died one day postdose. Observations at all other levels were not remarkable.

Project No. 2144-103 : Thirteen-Week Intra-articular Toxicity Study in Beagle Dogs

Three groups of beagle dogs (6/sex/group) received G.A.G.P.S. at dose levels of 2.0, 5.0 and 10.0 mg/kg of body weight by intra-articular injection three times a week for thirteen weeks. One high-dose male died but no significant differences in survival were noted between control and treated groups. Necropsy indicated compound-related gross pathology at the knee joints and injection sites of the treated groups. Compound-related histopathological alterations were observed. All lesions showed a reduction in severity and/or frequency with reduced dosage.

Project No. 2144-104 : Fertility Study in Female Rats

Three groups of twenty-four female rats received G.A.G.P.S. by daily intramuscular injection at dosages of 2.0, 8.0 or 32.0 mg/kg of body weight. The animals were observed for two weeks and then mated. Pregnancy rates and mean maternal body weights on Day 21 of lactation were decreased slightly in the treated groups relative to controls. Other maternal data were unremarkable. Dose-related trends significant in the high-dose group were noted in the cesarean-delivered litters. Mean body weights in the high-dose group of naturally delivered offspring of both sexes on Day 21 were significantly lower than control.

Project No. 2144-105 : Teratogenicity Study in Rabbits

The embryotoxic and teratogenic effects of G.A.G.P.S. were evaluated after intramuscular injection to pregnant rabbits at dosage levels of 2.0, 8.0 and 32.0 mg/kg of body weight. No significant effects were noted in pregnancy rates, corpora lutea, implantations, and visceral or skeletal anomalies and variants. The compound was found not to be teratogenic at levels up to 32 mg/kg during major organogenesis. At this level the compound was embryotoxic.

Project No. 2144-106 : Salmonella typhimurium Mammalian Microsome Plate Incorporation Assay

Under the conditions of this study, G.A.G.P.S. at levels up to 100,000 µg/plate was found not to be a mutagen.

Project No. 2144-107 : L5178Y Mouse Lymphoma Forward Mutation Assay

Under the conditions of this study, G.A.G.P.S. at dosage levels ranging from 100,000 to 1,000 µg/ml produced a dose-related toxic effect. No significant mutagenic activity was detected without activation. With the presence of an exogenous activation system, significant increases in mutation frequency were observed at three of the five dose levels.

Project No. 2144-108 : In-Vivo Cytogenetics Assay in Rats

G.A.G.P.S. was evaluated for its potential to induce structural aberrations in rat bone marrow cells. No significant increase in structural mutations in rat bone marrow cells was observed.

Project No. 2144-109 : Fertility Study in Male Rats

Three groups of twelve male rats received G.A.G.P.S. by daily intramuscular injection at dosage levels of 2.0, 10.0 and 25.0 mg/kg of body weight. The animals were treated for at least 60 days prior to and throughout the mating phase of the study. No significant differences between treated and control groups were observed.

In addition to these studies which were performed under laboratory conditions, a Sub-Acute Toxicity Study was done on horses. This study was performed by Research For Animal Health, of Fayettville, Arkansas. Dr. Doyne Hamm is president of this organization and personally supervised this study.

The purpose of this study was to evaluate the intra-articular treatment with PSGAG at dose levels of 1, 3, and 5 times the intended dosage of 250 mg/ml for a period of 3 times the recommended duration. Intra-carpal injections of PSGAG in sterile water were administered to three groups of horses every week at 250 mg, 750 mg, and 1,250 mg per horse respectively for 18 weeks. There were 18 horses in this study (9 males & 9 females). They ranged in age from 3 to 9 years.

At the time these horses were received, they were given a routine physical examination including clinical examination of the respiratory and cardiovascular systems and determination of vital signs. All animals were further examined for the following;

1. Fecal examination for paracites (if present, appropriate treatment for the specific paracite was given)
2. Hematologic examination (white blood count and hematocrit)
3. Vital signs (temperature, pulse and respiration)
4. Appetite (eats all, more than 50%, less than 50% or none of food provided)
5. Stool characteristics (normal, partially formed stool, diarrhea, stool loose and watery)
6. Presence or absence of cough or nasal discharge

Following clinical health screening, horses received encephalitis, rhinopneumonitis,and tetanus vaccines. All vaccines were administered by the study director.

Horses were kept in clean stalls and exercise lots. They were well fed with grain and hay and had fresh water avaliable at all times. Healthy animals were kept for a period of at least 10 days prior to being included in the study.After confirmation of their health and acclimation these animals were randomly assigned to one of 3 treatment groups of 3 geldings and 3 mares each.

The investigator who made the observations was not aware of the dose administered to each horse. This procedure was used to control bias. Observations were made immediately before the drug was given. Biologic samples were immediately refrigerated and then submitted to an accredited laboratory on the same day for analysis.

Clinical observations at the end of the trial showed a dose related soreness in the 750 mg and the 1,250 mg groups at the injection site. This soreness was mild and lasted only one or two days.

Laboratory data indicated a dose related effect on several blood parameters (partial prothrombin time, creatinine, and glucose) which were slightly elevated. These changes in blood parameters were not considered to be medically significant in the judgement of the study director.No animal appeared to have any clinical illness during this study and none showed any signs of toxicity except for transient swelling at the site of injection, which was not due to infection.

This study indicates that at the recommended dosage of 250 mg no signs of toxicity will be seen. At much higher doses, for extended periods of time, signs of toxicity are not severe, are self limiting and are reversible.

Use in Breeding Animals

The following statement appears in the product labeling:

Impairment of Fertility studies in mares and stallions have not been conducted. Do not use in horses intended for breeding.

6. Human Safety

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This drug is approved for use only in horses that are not to be used for food and is to be labeled:

Warning: Not for use in horses intended for food.

Human safety relative to possession, handling and administration: No special caution statement needed.

7. Agency Conclusions:

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that Adequan (polysulfated glycosaminoglycan) when used under its labeled conditions of use is safe and effective.

The safe and effective use of Adequan (polysulfated glycosaminoglycan) injected intra-articularly in horses requires a surgical technique and knowledge of the anatomy of the specific equine joint. We have concluded that the expertise of a veterinarian is necessary for proper administration of the drug. Accordingly, we have classified Adequan (polysulfated glycosaminoglycan) as a prescription item.