Approval Date: November 11, 1989

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-901

B. Sponsor

Luitpold Pharmaceuticals, Inc.
One Luitpold Drive
Shirley, New York 11967

C. Proprietary Name

Adequan® i.m.

D. Established Name

Polysulfated Glycosaminoglycan (PSGAG)

E. Dosage Form, Route of Administration and Recommended Dosage

The recommended dose of Adequan® i.m. in horses is 500 mg every 4 days for 28 days intramuscularly. The injection site must be thoroughly cleansed prior to injection. Do not mix Adequan® i.m. with other drugs or solvents.

F. Indication

Adequan® i.m. is recommended for the intramuscular treatment of noninfectious degenerative and/or traumatic joint dysfunction and associated lameness of the carpal joint in horses.

II. EFFECTIVENESS

Adequan® i.m. for the treatment of lameness in horses, has been evaluated in both a dose titration study and in field trials. These two pivotal studies were adequate and well controlled. There were 36 horses studied in the dose titration investigation and 43 horses in the field trials.

Pivotal Study 1.

Dose Titration Investigation

The dose titration investigation was performed by Drs. Doyne Hamm and Gary White of Fayetteville, AR. 72701. Dr. E. Wynn Jones of Mississippi State University served as the quality control director of this study. This study was conducted on a blinded 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 intramuscular administration of Adequan® i.m. The model used produces:

1. A syndrome which is pathologically compatible with the use of Adequan® i.m.

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.

4. Characteristics which provide for confirmation of the syndrome (e.g. joint fluid and necropsy parameters).

Healthy, mature animal of quarter horse or thoroughbred type served as experimental animals. These animals were acclimated to the environment, maintained in covered stalls and 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, limping and osteitis.

The various treatments comprises sterile saline solution as a placebo control, and 50 mg, 125 mg, 250 mg, 500 mg, and 1,000 mg of the active drug substance Adequan® i.m. dissolved in sterile water. Injections were given once every 4 days for a total of 7 injections. Treatment followed a 10 day acclimation period, and a five day model induction period. The study was conducted in replicates of six in which all treatment groups were represented. There were six horses per group for a total of 36 horses.

Observations consisted of the following:

1. clinical - temperature, pulse and respiration

2. lameness (once weekly) prior to treatment

    a. angle of carpal flexion

    b. maximum angle of carpal flexion permitted

    c. length of stride (lame limb)

3. limb circumference

4. joint fluid - total protein at time of each treatment

5. radiograph - pretreatment and at study conclusion

6. hemogram - red and white blood cell count/hematocrit/hemoglobin, once weekly
7. necropsy - gross and histological observations. The data collected for this study comprises two categories:

    a. daily-weekly observations and

b. b.measurements for carpal volume calculations.

The mean response for each of the variables, temperature, pulse, respiration, flexion at rest, maximum flexion allowed, stride at rest, stride after exercise, limb circumference, joint fluid total protein, white blood cell count, red blood cell count, hematocrit, and hemoglobin was calculated for each of the five dose groups.

Analysis of variance was performed to test for dose effect. Duncan's multiple range test was performed for those variables showing a significance level of 0.05 or less.

The parameter abbreviations used in Tables 1, 2, 3 and 4, the manner of grouping similar and different groups, and the designations for the various groups are specified as follows.

DFL-MAX = Maximum carpal flexion permitted in degrees

DSTD-RST = Stride length (lame leg) after rest in inches

DSTD-EXR = Stride length (lame leg) after standard exercise in inches

D-CIRCUM = Circumference of affected joint in centimeters

D-PRTN = Synovial fluid protein level in mg/mL (affected joint)

The doses represent:

0 = placebo control

1 = 50 mg Adequan®

2 = 125 mg Adequan®

3 = 250 mg Adequan®

4 = 500 mg Adequan®

5 = 1,000 mg Adequan®

The values within the same brackets are not statistically different at the .05 level. That means 5 chances or less in 100 that these differences are the result of chance.

Table 1. indicates the overall analysis of change from baseline data:

Table 1

Variable	**Significance Level for Dose**	**Duncan's Test for Dose**
DFL - MAX	.0001	(5,4) (3,1,2,0)
DSTD - RST	.0505	(4,5,3,2) (5,3,2,0) (3,2,0,1)
DSTD - EXR	.0001	(5,4) (3,2,0,1)
D-CIRCUM	.0086	(0,1,3,2) (2,5) (5,4)
D-PRTN	.0155	(1,0,3,2) (5,4)

The results from the analysis of the change from baseline data on treatment days are indicated in Table 2, entitled Duncan's Test for Dose on Treatment Days:

Table 2 (Dose groups are the same as Table 1 page 4)

Variable	Treatment Day – 2	Treatment Day - 3	Treatment Day - 4	Treatment Day – 5	Treatment Day - 6
DFL - MAX	(4,5) (5,1) (1,2,3,0)	(5,4) (4,3,2) (3,2,1) (2,1,0)	(4,5) (3,1,2,0)	(5,4) (3,1,2,0)	(5,4) (2,1,3,0)
DSTD - RST		(4,5,3,2,1) (3,2,1,0)	(4,5) (5,3,0,2,1)	(5,4) (3,2,0,1)	(5,4) (0,2,3,1)
DSTD - EXR	(5,4,3) (3,0,2,1)	(5,4) (3,2,1,0)	(4,5) (3,0,2,1)	(4,5) (2,3,0,1)	(5,4) (2,3,0) (3,0,1)
D-CIRCUM		(0,1,3,2) (4,5)	(0,1,3,2) (5,4)	(0,1,2,3) (5,4)	(0,3,1,2) (5,4)
D-PRTN	(2,0,3,1) (0,3,1,4,5)	(1,0,2,3) (5,4)	(1,2,3,0,5) (5,4)	(0,1,3,2) (1,3,2,4,5)	(3,1,2,0) (5,4)

Statistically the dosages of 500 mg and 1,000 mg are not different. The other dosages (placebo, 50 mg, 125 mg and 250 mg) have been demonstrated to be statistically different from the 500 and 1,000 mg groups but the same as each other. These conclusions were highly statistically significant. The analysis of the carpal volume changes are summarized in Table 3. (Dose groups are the same as Table 1 page 4)

Table 3

Variable	Significance Level for Dose	Duncan's Test for Dose
Volume Change	.0004	(0,1,3,2) (4,5)
Percent Vol. Change	.0004	(0,1,3,2) (4,5)

Measurements for carpal volume calculations were taken at the beginning, middle and end of the experiment. Changes of the affected carpal volume that occurred from the beginning to the end of the experiment were analyzed. The chances that these results were a matter of chance are 4 in 10,000. Table 4. represents the results from the analysis of the change from baseline data on the various treatment days. (Abbreviations for variables are the same as those specified for Table 1 page 4).

Table 4

Variable	Treatment Day – 0	Treatment Day – 1	Treatment Day – 2	Treatment Day – 3	Treatment Day – 4	Treatment Day – 5	Treatment Day – 6
DFL - MAX	.9821	.4565	.0065	.0006	.0001	.0001	.0001
DSTD - RST	.8073	.9978	.1563	.0412	.0568	.0004	.0007

Variable	Treatment Day – 0	Treatment Day – 1	Treatment Day – 2	Treatment Day – 3	Treatment Day – 4	Treatment Day – 5	Treatment Day – 6
DSTD - EXR	.7815	.3255	.0012	.0001	.0001	.0001	.0001
D-CIRCUM	.7824	.8351	.3635	.0019	.0058	.0024	.0004
D-PRTN	.4930	.4360	.0261	.0005	.0556	.0846	.0040

An examination of Tables 2, 3 and 4 reveals that, with time, the various treatment levels (dosages) become grouped. The groupings by treatment day 6 (7th injection) invariably reveal that the 500 mg and 1,000 mg doses have the same response which is superior to other, lower doses. The statistical significance of these findings range from 4 chances in 1,000 (D-PRTN) to 1 chance in 10,000 (DFL-MAX, DSTD-EXR). As a means of confirming the results stated above an analysis of variance, LSD pair-wise comparisons and linear-plateau and polynomial regression model fitting were done on the variables maximum flexion, stride at rest, stride after exercise, circumference, protein, carpal volume change and percent volume change at the final measurement minus the base line measurement. A blocking term and a block by treatment interaction term were included in the analysis of variance model since the study was done in three replicates of 12 animals per replicate.

The overall analysis of variance showed that the treatment means were significantly different and pair-wise comparisons showed that there was no significant difference ($p > .05$) between the means of the two highest doses----500 mg & 1,000 mg---but that there were significant differences ($p < .05$) between the means of the two highest doses and the three lowest doses and the placebo ($p < .05$ means less than a 5 out of 100 probability these findings are due to chance). For all the variables, except stride at rest, this was a reasonable fitting model. This model is a plateau between the placebo and the three lowest doses (50 mg, 125 mg, 250 mg), and a straight line between the 250 mg dose and the 500 mg dose and a plateau from the 500 mg dose through the highest dose (1,000 mg).

The conclusion that can be drawn from this dose titration study is that for the parameters associated with lameness i.e. flexion, stride length, joint circumference and synovial fluid protein levels, 500 mg of Adequan® i.m. is the optimal dosage. The possibility that this finding is a product of chance is about one in ten thousand. At this dosage one would not expect to find any harmful effects on the bone or cartilage or systemically.

Pivotal Study 2

Clinical (Field) Trials

The following investigators participated in the controlled field trials to compare the efficacy of Adequan® i.m. versus Adequan intra-articular.

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Doyne Hamm, DVM
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Research for Animal Health, Inc.
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Tracy A. Turner DVM, MS
Assistant Professor of Surgery
Dept. of Surgical Sciences
College of Veterinary Medicine, Large Animal Hospital
University of Florida
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The participating veterinarians are suitably qualified by their training and experience to investigate the effectiveness of drugs used to treat lameness in horses.

The purpose of this study was to demonstrate that Adequan® i.m., when used under field conditions, had the same beneficial characteristics as were shown during the dose titration study and to compare these effects to the already marketed Adequan intraarticular. Thus, Adequan intraarticular was the active treatment control. We refer here to the safety and efficacy data from the approved NADA 136-383 for Adequan intraarticular (49 FR47829; Dec. 7, 1984).

Diagnosis of carpal joint lameness was based on expert objective evaluation and, where possible, confirmed by radiography. Synovial fluid analysis had to show either elevated protein levels or decreased viscosity levels for the animal to qualify.

Twenty four horses received intraarticular injections (250 mg Adequan® each, once a week for 5 weeks) and 19 horses received intramuscular injections (500 mg Adequan® each once every four days for 28 days).

The following parameters were evaluated:

1. lameness at a walk (graded 0-3)
2. lameness at a jog (graded 0-3)
3. pain on palpation of the articular margin (graded 0-3)
4. maximum flexion permitted (0 = <= 30°, 1 = 31-60°, 2 = 61-90°, 3 = >90°)
5. swelling of the joint (graded 0-3)
6. heat (graded 0-2)
7. synovial fluid protein (gm/dL)
8. synovial fluid viscosity
9. overall clinical evaluation of response (excellent, good, fair,poor)

Table 5 is a tabulation of the results of the study: mean response value in above indicated parameters

Table 5

Variable	**Adequan® i.m. group - Initial**	**Adequan® i.m. group - Final**	**Adequan® ia group - Initial**	**Adequan® ia group - Final**
Lameness Walk	0.684	0.000	0.783	0.000
Lameness Jog	1.211	0.125	1.348	0.136
Pain on palpation LF	1.667	0.118	0.318	0.045
Flexion LF	2.111	2.706	2.391	2.619
Swelling LF	1.778	0.235	0.783	0.348
Pain on Palpation RF	0.611	0.000	1.000	0.000
Flexion RF	2.222	2.235	1.857	2.857
Swelling RF	1.000	0.118	1.381	0.190
Heat	1.105	0.444	1.318	0.364
Synovial Fluid Protein	1.805	2.026	1.930	1.935
Synovial Fluid Viscosity	4.158	7.732	4.391	5.948

The overall response as judged by the investigators is shown in Table 6:

score	**im**	**ia**
Excellent	36.8%	41.6%
Good	52.6%	45.8%
Fair	10.5%	8%
Poor	0%	4%

Statistical tests (analysis of variance) were conducted to compare treatment groups. Table 7 lists the variable and the probability (p) values. A p-value of 0.05 or less was considered to demonstrate a statistically significant difference between the response in the ia and im groups.

Table 7

Variable	**p-value**
Lameness at a walk	0.4239
Change in lameness at a walk	0.4239
Lameness at a jog	0.7718
Change in lameness at a jog	0.3660
Pain on palpation	0.4895
Change in pain on palpation	0.7668
Pain on flexion	0.2884
Change in pain on flexion	0.3217
Swelling	0.2900
Change in swelling	0.4061
Heat	0.2122
Change in heat	0.0960
Synovial fluid protein	0.7538
Synovial fluid viscosity	0.2634

Variable	**p-value**
Final overall evaluation	0.6766

Tables 5-7 demonstrate a response to therapy with Adequan® i.m. which was indistinguishable both clinically and statistically from the response to therapy with Adequan intraarticular in clinical cases of carpal joint dysfunction.

No adverse reactions to Adequan® i.m. were recorded.

Corroborative Study

An open field trial (uncontrolled) was also performed. The following investigators, suitably qualified by training and experience to evaluate the efficacy of a drug for treatment of equine lameness, participated in the trials.

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William E. Riddle, VMD
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Steven R. Weeks, DVM
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The purpose of the study was to gain additional support for the safety and efficacy of Adequan® i.m. when used under field (racetrack) conditions.

The diagnosis of carpal joint lameness was based on expert objective evaluation and where possible confirmed by radiography. Adequan® i.m. injections (500 mg) were administered intramuscularly every 4 days for 28 days. Parameters evaluated were the same as for the pivotal field trial except synovial fluid protein and viscosity were excluded (see page 9). Forty two cases were treated in the study. The overall evaluation as judged by the investigators revealed the following responses:

•Excellent 40.5%

•Good 40.5%

•Fair 9.5%

•Poor 9.5%

The results of the overall evaluation in this study are comparable to the results achieved in the controlled field trials. No adverse reactions were reported. Thus this study yielded further support for the safety and efficacy of Adequan® i.m. under the proposed conditions of use.

III. TARGET ANIMAL SAFETY

Adequan® i.m. for the treatment of non-infectious degenerative and/or traumatic joint dysfunction and associated lameness of the equine carpal joint has been evaluated in a pivotal subacute toxicity study in horses. In addition 10 preclinical studies by Hazelton Laboratories of Vienna, VA 22180, and a controlled field study involving 3 investigators provided corroborative evidence of safety.

There was no meaningful evidence from any of these studies that indicated that the active ingredient in Adequan® i.m. (PSGAG) has clinically relevant toxic properties.

Pivotal Study

A subacute toxicity study was done on horses. This study was performed by Research for Animal Health, of Fayetteville, Arkansas. Dr. Doyne Hamm is President of this organization and personally supervised this study.

The purpose of this study was to evaluate the intramuscular treatment with PSGAG at dose levels of 1, 3 and 5 times the intended dosage of 500 mg for a period of 3 times the recommended duration. Intramuscular injections of PSGAG in sterile water were administered to three groups of horses every 4 days at 500 mg, 1,500 mg and 2,500 mg per horse respectively for 12 weeks. There were twenty-four horses in this study (14 females 9 geldings and 1 male). Their weights ranged from 600 to 972 lbs. and their ages from 2 to 10 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 measurements:

1. Fecal examination for parasites
2. Hematologic examination
3. Temperature, pulse, respiration
4. Appetite
5. Stool characteristics (physical)
6. Presence or absence of nasal discharge or cough.

Following clinical health screening, horses received encephalitis and rhinopneumonitis vaccines and were treated for parasitism. All vaccines were administered by the study director. Horses were kept in clean stalls. They were well fed with grain and hay and had fresh water available 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 four treatment groups of 6 horses each.

The following parameters were measured over the course of the study:

1. Daily observations:

    ◦Body temperature
    ◦Pulse
    ◦Respiration
    ◦Cough (presence/absence)
    ◦Nasal discharge (presence/absence)
    ◦Stool characteristics (physical)
    ◦Appetite

- Attitude

2. Measured every 4 days:

   - White blood cell count and differential Red blood cell count
   - Platelet count
   - Hemoglobin
   - Hematocrit
   - Partial thromboplastin time

3. Measured every 21 days:

   - Blood urea nitrogen (BUN)
   - Total protein
   - Bilirubin
   - Alkaline phosphatase
   - Sodium
   - Potassium
   - Creatinine
   - SGPT
   - Albumin/globulin ratio
   - Urine pH
   - Urine protein
   - Urine glucose
   - Urine ketone
   - Urine bilirubin
   - Urine blood
   - Urine urobiliningen
   - Urine specific gravity
   - Urine bile pigments
   - Urine bile salts

4. Measured at days 0, 42 and 83

   - Body weight

5. Measured on day 0 and day 84

   - Bromsulphalein clearance from venous blood

No clinically significant changes occurred in any of the laboratory parameters or the clinical signs. At the onset of the study the mean body weight was 736 ± 94 lbs. At day 43 the mean body weight was 790 ± 78 lbs. At day 83 the mean body weight was 836± 69 lbs. The weight gain was also reflected in an appearance of good general body condition. Table 1 lists the parameters along with the results of the analysis of variance to detect dose group differences. For those parameters in which significant dose group differences were detected, the results of Duncan's multiple range test to separate groups appear in parenthesis. A p value of <0.05 was considered significant. Dosage groups were:

0 = placebo group

1 = 500 mg Adequan® i.m.

2 = 1,500 mg Adequan® i.m.

3 = 2,500 mg Adequan® i.m.

PARAMETER	**P-VALUE**	**(DUNCAN'S GROUPINGS)**
Body temperature	NS	
Pulse	NS	
Respiration	NS	
Cough	NS	
Nasal discharge	NS	
Stool characteristics	NS	
Appetite	NS	
Attitude	NS	
Red blood cell count	NS	
White blood cell count	0.0503	(1,3,0) (3.0,2)
Polymorphonuclear cells	0.0157	(1) (3,2,0)
Band cells	NS	
Lymphocytes	0.0257	(1) (3,2,0)
Monocytes	NS	
Eosinophils	NS	
Basophils	NS	
Red blood cell count	NS	
Platelet count	NS	
Hemoglobin	NS	
Hematocrit	NS	
Partial thromboplastin time	NS	
Blood urea nitrogen (BUN)	NS	
Total protein	NS	
Bilirubin	NS	
Alkaline phosphatase	NS	
Sodium	NS	
Potassium	NS	
Creatinine	NS	
SGPT	NS	
Albumin/globulin ratio	NS	
Urine pH	NS	
Urine protein	NS	
Urine glucose	NS	
Urine ketones	NS	
Urine bilirubin	NS	
Urine blood	NS	
Urine urobilinogen	NS	
Urine specific gravity	NS	
Urine bile pigment	NS	
Urine bile salts	NS	
Body weight	NS	
Bromosulphthalein clearance	NS	

The significant group differences detected for white blood cell counts, polymorphonuclear cells and lymphocytes do not appear to be dose related as reflected by the Duncan's groupings. No adverse reactions to the injections were noted. This study shows that at the recommended dosage of 500 mg no sign of toxicity will be seen. At much higher doses for extended periods of time there are no signs of toxicity.

Corroborative Studies

Preclinical studies performed by Hazelton Laboratories include the following:

1. Acute Intravenous Toxicity Study in Rats
2. Thirteen Week Toxicity Study in Ratis
3. Acute Intravenous Toxicity Study in Dogs
4. Thirteen week Intra-articular Toxicity Study in Dogs
5. Fertility Study in Female Rats
6. Teratogenic 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 follow:

PSGAG (POLYSULFATED GLYCOSAMINOGLYCAN PRECLINICAL INVESTIGATIONS)
Project No. 2144-100: Acute Intravenous Toxicity Study in Rats

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

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

The subchronic toxicity following daily administration by intramuscular injection for four or thirteen weeks in male and female rats at dose levels of 2, 10 and 25mg/kg of body weight was determined. One high dose (25mg/kg) 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 hematocyst were observed in muscles from high-dose males and females. This finding suggests that PSGAG 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 PSGAG in male and female beagle dogs was evaluated at dose levels of 0.25, 0.50, 1.0 and 2.0g/kg of body weight. The 2.0g/kg male died one day post-dose. 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 PSGAG at dose levels of 2.0, 5.0 and 10.0mg/kg of body weight by intraarticular 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 PSGAG by daily intramuscular injection at dosages of 2.0, 8.0 or 32.0mg/kg of body weight. The animals were observed for two weeks and then mated. Pregnancy rate 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 groups were noted in the cesarean delivered litters. Mean body weights in the high-dose group of naturally delivered offspring of both sexes on Day 2 were significantly lower than control.

Project No. 2144-105: Teratogenic Study in Rabbits

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

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

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

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

Under the conditions of this study, PSGAG at dosage levels ranging from 100,000 to 1,000µg/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

PSGAG 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 PSGAG by daily intramuscular injection at dosage levels of 2.0, 10.0 and 25.0mg/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.

Reproduction

The following statement appears in the product labeling:

"Studies have not been conducted to establish safety in breeding horses."

IV. HUMAN FOOD SAFETY

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

Human Safety Relative to Possession, Handling and Administration

The labeling contains adequate caution statements, i.e. "Keep this and all medications out of the reach of children."

V. AGENCY CONCLUSIONS

Adequan® i.m. (polysulfated glycosaminoglycan)

This NADA is supported by data that satisfy with the requirements set forth in Section 512 of the Act and 21 CFR 514.111 of the regulations. Those data reveal that when Adequan® i.m. is used according to the conditions set forth in the labeling, it is a safe and effective medicament.

In order to use Adequan® i.m. properly, the diagnosis of degenerative or traumatic joint dysfunction and associated lameness must be made. Only a veterinarian, suitably qualified

by training and experience can make such a diagnosis. Therefore the drug product is classified as a prescription drug.

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.