Approval Date: September 12, 1996

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 by intramuscular injection. 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 and hock joints in horses.

G. Effect of Supplement

Effect of Supplement: This supplemental application amends the NADA to provide for the use of Adequan® i.m. in the treatment of noninfectious degenerative and/or traumatic joint dysfunction and associated lameness of the hock joint in horses.

II. EFFECTIVENESS

Pivotal Study

Comparison of PSGAG levels in the synovial fluid of the equine carpus and hock joints after a single intramuscular injection of 500 mg 3HPSGAG

This study was performed to compare the levels of PSGAG achieved in the synovial fluid of the equine carpus and hock joints after a single intramuscular injection of 500 mg 3HPSGAG.

The study was performed at the Boren Veterinary Teaching Hospital of Oklahoma State University at Stillwater, Oklahoma. Investigators included:

Michael A. Collier, DVM, DACVS
Boren Veterinary Medical Teaching Hospital
Study Director

Mark Haugland, DVM
Boren Veterinary Medical Teaching Hospital
Research Associate

Flavio Sequeria, Med Vet
Boren Veterinary Medical Teaching Hospital
Research Associate

Lawrence DeBault, Ph.D., Department of Pathology at Oklahoma University Medical Center, Oklahoma City, Oklahoma, performed all liquid scintillation analyses. Peter Panse, MD of the pharmacokinetics department of Luitpold Pharma GmbH was responsible for preparation of the test drug.

The purpose of this study was to determine the levels of PSGAG achieved in the equine hock joint following a single intramuscular injection of 500 mg PSGAG, and to compare these levels to those achieved in the equine carpus.

Eight healthy mature horses 2 years old to aged (4 geldings, 2 stallions, 2 mares) (5 Quarterhorses, 2 Thoroughbreds, 1 Paint) served as test animals. The horses had no clinical evidence of degenerative joint disease.

The test drug was tritium labeled PSGAG prepared by Dr. Peter Panse. Each ampule contained 1 mL of a solution of 500 mg 3HPSGAG with a total radioactivity of 2.0447 mCi per ampule. The test drug was administered by intramuscular injection into the lateral cervical region. Synovial fluid samples were collected by aseptic arthrocentesis from the carpus and hock joints prior to injection of the radiolabeled drug and at 2, 4, 8, 12, and 24 hours after injection.

Samples were subjected to liquid scintillation analysis. The values from the liquid scintillation (expressed as decays per minute per 200 L) were converted to g PSGAG/mL synovial fluid. The results are summarized in table one:

Table One Group Means: Synovial Fluid PSGAG Level (g/mL)

Joint	**2 Hrs**	**4 Hrs**	**8 Hrs**	**12 Hrs**	**24 Hrs**
Carpus	0.971	0.595	0.388	0.131	0.077
Hock	0.655	0.565	0.375	0.165	0.098

In order to assess the bioequivalence in the PSGAG levels of the hock joint relative to that of the originally approved carpal joint, the area under the curve was calculated by integrating a smooth nonlinear regression line. The equation selected for fitting describes the concentration of an intermediate B in the compartmental model A -> B <-> C, with all rate constants fit as first order rate constants. The AUC was calculated using only the actual data points, and not extrapolated through the "tail area". These values were analyzed using a paired samples t-test since each horse contributed an area for each synovial fluid type.

Table Two Mean area under the curve and standard deviations for the two joints

	Carpal joint	Hock joint
Mean area under the curve	6.649	6.528
(standard deviation)	(2.46)	(2.85)

Using the calculated area under the curve values, a 90% confidence interval was calculated on the difference between the areas under the curve of the synovial fluid for the carpal joint and the hock joint. The 90% confidence intervals used the standard deviation of the paired t-test as the error estimate. In order to show bioequivalence, the confidence interval should lie within +/- 20% of the reference mean, i.e., the carpal joint. As shown in table 3 below, this is true for the carpal and hock joints.

Table Three Confidence bounds for differences between carpus and hock joints

Pair	Mean Difference of Joint Synovial Fluid	Standard Deviation	90% Confidence Lower Bound	90% Confidence Upper Bound
Hock minus carpal joint	-0.121521	1.733866	-19.30%	15.64%

Conclusions drawn from this study were:

1. Drug levels achieved in the hock were bioequivalent to those in the carpus.

2. The efficacy of Adequan i.m. in the treatment of non-infectious degenerative and/or traumatic joint dysfunction of the equine carpal joint has been demonstrated in clinical trials. It is reasonable to assume that equivalent efficacy would be expected in the treatment of non-infectious degenerative and/or traumatic joint dysfunction of the equine hock joint, since drug levels in the carpus and hock are bioequivalent.

Corroborative Study

Radiolabeled Pharmacokinetic Study of Adequan® i.m. in the Horse

This study was a pharmacokinetic study of tritium-labeled PSGAG which examined serum, carpal synovial fluid, and carpal articular cartilage levels of the drug after intramuscular injection. The study also examined the effect of Adequan intraarticular injections on hyaluronic acid levels in the carpal synovial fluid.

The study was performed at the Boren Veterinary Medical Teaching Hospital of Oklahoma State University. The following investigators participated in the study:

Dr. Michael A. Collier
Boren Veterinary Medical Teaching Hospital
Oklahoma State University
Stillwater, OK
Principal Investigator

Dr. Daniel Burba
Boren Veterinary Medical Teaching Hospital
Oklahoma State University
Stillwater, OK
Research Associate

Dr. Lawrence DeBault
School of Medicine
University of Oklahoma
Oklahoma City, OK
Scintigraphy of serum, urine, and synovial fluid samples

Dr. Olivia Hanson-Painton
Boren Veterinary Medical Teaching Hospital
Oklahoma State University
Stillwater, OK
Synovial fluid analysis and hyaluronic acid assays

Dr. Peter Panse
Luitpold-Werk
Munich, West Germany
Scintigraphy of articular cartilage and bone; preparation of the radiolabeled PSGAG

The purpose of this study was to determine serum, urine, and synovial fluid PSGAG levels after intramuscular injection of 500 mg of tritium-labeled PSGAG (3HPSGAG) at selected intervals and to assay bone and cartilage levels at 96 hours post injection. Synovial fluid parameters including hyaluronic acid content were also determined at selected intervals. The effect of an induced cartilage lesion was also examined on the kinetics of the drug when compared to its distribution in the normal synovial joint.

Eight mature horses (2-14 years of age, 3 geldings, 5 females; 7 Quarterhorse, 1 Appaloosa) which were determined to be healthy and free of carpal joint disease were utilized in the study. A defect was created in the distal dorsal medial articular surface of the left radial carpal bone by means of an arthoburr via arthroscopy. The right carpus served as a normal joint for comparison. The horses were allowed to recover for at least 12 days prior to administration of the radiolabeled drug.

The test drug contained 500 mg of PSGAG labeled with tritium. The specific radioactivity of the solution was 1.739 mCi per mg of PSGAG for a total of 881 mCi per 500 mg dose. The test drug was prepared by Dr. Peter Panse at Luitpold-Werk in Munich, West Germany.

The test article was administered by intramuscular injection into the lateral cervical area. The dose used in the study was 500 mg. After injection the horses were observed for 96 hours and the various tissue fluids were collected. The horses were euthanized 96 hours post-injection and cartilage and bone tissues were collected.

The following parameters were examined:

1. Serum, urine and carpal synovial fluid 3HPSGAG levels at 0, 2, 4, 8, 12,24, 48, and 96 hours after injection.

2. Carpal synovial fluid for hyaluronic acid levels at 0, 2, 4, 8, 12, 24, 48, and 96 hours after injection.

3. Carpal synovial fluid for routine clinical analysis prior to arthroscopy and 96 hours after injection.

4. Cartilage and subchondral bone samples at 96 hours for 3HPSGAG content.

All synovial fluid, cartilage and bone samples were collected from both the target joint (damaged left carpus) and the contralateral normal joint (right carpus). Two cartilage and subchondral bone samples were taken from the radial carpal bone of each joint. These included a sagittal section through the area of the lesion on the left carpus and a similar area of the right carpus. The remaining distal radial carpal bone cartilage was collected from each knee and designated as the distal sample.

The results of the study are presented in Tables four to eight.

Table Four: Mean Serum 3HPSGAG Levels

Hour	UG 3HPSGAG/ML SYNOVIAL FLUID
0	0.00
2	1.958
4	1.184
8	0.380
12	0.179
24	0.101
48	0.107
96	0.118

Table Five: Mean Urine 3HPSGAG Levels

Hour	UG 3HPSGAG/ML URINE
0	0.00
2	173.610
4	137.035
8	55.128
12	18.995
24	4.753
48	2.954
96	1.692

Table Six: Mean Carpal Synovial Fluid 3HPSGAG Levels

Hour	UG 3HPSGAG/ML SYNOVIAL FLUID LEFT CARPUS	UG 3HPSGAG/ML SYNOVIAL FLUID RIGHT CARPUS
0	0.00	0.00
2	0.331	0.248
4	0.296	0.276
8	0.054	0.107
12	0.042	0.059
24	0.039	0.034
48	0.043	0.062
96	0.081	0.086

Table Seven: Mean Hyaluronate Concentrations

Hour	MG HYALURONATE/ML SYNOVIAL FLUID LEFT CARPUS	MG HYALURONATE/ML SYNOVIAL FLUID RIGHT CARPUS
0	0.438	0.476
2	0.417	0.446
4	0.402	0.414
8	0.448	0.487
12	0.494	0.488
24	0.653	0.660
48	0.933	0.931
96	0.775	0.866

Table Eight: Overall Mean 3HPSGAG Levels in Cartilage and Bone

Hour	UG 3HPSGAG/G CARTILAGE	UG 3HPSGAG/G BONE
96	0.201	0.124

Statistical analysis of the data included:

1. Analysis of serum, urine, and synovial fluid 3HPSGAG values for both knees using a one-compartment open pharmacokinetic model for i.m. injections. Synovial fluid 3HPSGAG values over time and between right and left carpi were compared by means of repeated ANOVA. Serum and synovial fluid drug levels were highly correlated over time. No statistically significant differences between synovial fluid levels in the right and left carpus were detected at any time.
2. Hyaluronic acid levels in the synovial fluid were compared over time in both the left and right carpus. Table nine summarizes the p-values in both the left and right carpus at 24, 48 and 96 hours versus the 0 hour baseline.

   Table Nine

Time Post Baseline	Left Carpus	Right Carpus
24 hours	0.008	0.041
48 hours	0.001	0.029
96 hours	0.012	0.028

   There were no statistically detectable differences between the right and left carpus.

3. A factorial analysis of variance was performed on cartilage and bone samples taken at 96 hours. Factors included time (half the samples were analyzed for radioactivity at a later time after the experiment), location (sagittal versus distal) and side (left versus right). No statistically significant differences were detected between left and right or sagittal and distal sections.
4. Relationships between pharmacokinetic parameters and 3HPSGAG levels in the various tissues and hyaluronic acid levels in the synovial fluid were investigated by correlation and regression analysis. No significant correlations were found.

Conclusions drawn from the study include:

1. PSGAG is systemically absorbed and distributed via the bloodstream.

2. The normal carpal joint and the joint with the surgically created defect responded in a similar fashion with slightly greater increases noted in the joint with the damaged cartilage.

3. Serum and synovial fluid 3HPSGAG were highly correlated over time after intramuscular injection.

4. Injection of 500 mg of PSGAG led to a statistically significant increase in synovial fluid hyaluronic acid content at 24, 48 and 96 hours after injection in both the target and control joint. Based on the data from the Pivotal Study above, this should also occur in equine hock joints.

No adverse reactions were noted in this study.

III. ANIMAL SAFETY

Information concerning the safety of Adequan® i.m. is contained in the existing FOI Summary for this product (NADA 140-901, 21 CFR 522.1850).

This supplemental approval uses the same dose and route of administration of Adequan® i.m. as in the original application. Therefore, no additional safety studies were required.

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 for approval of this supplemental 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

This supplemental NADA is supported by data that comply with the requirements set forth in Section 512 of the Act and 21 CFR 514.111 of the regulations. These 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.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. This supplement provides for the additional claim to include the treatment of

noninfectious degenerative and/or traumatic joint dysfunction and associated lameness of the hock joint in horses. The approval of this change relied on the safety and effectiveness data in the parent application and evaluation of new efficacy data submitted in the supplemental application.

In order to use Adequan® i.m. properly, the diagnosis of degenerative or traumatic hock 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.