Approval Date: September 12, 1991

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-883

B. Sponsor

MOBAY Corporation
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201

C. Proprietary Name

Legend™ (Hyaluronate Sodium) Injectable Solution

D. Product Established Name

Hyaluronate Sodium

E. Dispensing Status

Rx

F. Dosage Form, Routes of Administration and Recommended Dosages

Intravenous - 4 mL (40 mg). Intra-articular - 2 mL (20 mg) in the carpus or fetlock. Treatment may be repeated at weekly intervals for a total of three treatments.

Strict aseptic technique should be observed when administering by intra-articular injection. As with any intra-articular procedure, proper injection site disinfection and animal restraint are important. Excess joint fluid should be aseptically removed prior to injection. Care should be taken to avoid scratching the cartilage surface with the tip of the injection needle. Diffuse swelling lasting 24 to 48 hours may result from movement of the needle while in the joint space.

For intravenous administration, use aseptic technique and inject slowly into the jugular vein.

Horses should be given stall rest after treatment before gradually resuming normal activity.

Discard any unused portion of the drug and the empty vial after opening.

G. Indications for Use:

Legend Injectable Solution is indicated in the treatment of joint dysfunction of the carpus or fetlock in horses due to non-infectious synovitis associated with equine osteoarthritis.

II. STUDIES DEMONSTRATING EFFECTIVENESS

A. Pivotal Studies

1. Dose Titration – Intra-articular Injectable Solution

A dose titration study was conducted by Dr. Doyne Hamm, at Research for Animal Health, Fayetteville, Arkansas, from March to August, 1985.

a. Study Design

This study was designed to determine the effective dose of Legend Injectable Solution, a 1% injectable solution of MOBAY hyaluronate sodium for intra-articular therapy of experimentally induced carpitis of the horse. Thirty-six horses of Quarter Horse type were divided into six treatment groups (six horses each): 1) Phosphate Buffered Saline, negative control (2 mL); 2) 5 mg Legend Injectable Solution (0.5 mL); 3) 20 mg (2 mL); 4) 40 mg (4 mL); 4) 20 mg repeated in two weeks (2 mL-2 mL); 6) positive control commercial product (Hylartin-V, 2 mL). The Test Drug was the formulation intended for market. Each horse was treated once in the Intercarpal joint except for group 5 which received two injections in the intercarpal joint at a two week interval. Five days prior to treatment, lameness was induced in each horse using Freund's Complete Adjuvant.

The study was blinded by using two veterinarians. One administered drug treatment and the other conducted the evaluation and did not know which treatment each animal received.

Evaluations were made at the day of induction of lameness and every other week starting at the time of treatment. Measurements included: body temperature, pulse rate, respiration rate, lameness score, standing leg angle, flexed leg angle, range of motion, stride after rest, stride after exercise, cast volume, joint circumference, white blood cells, joint fluid protein, and joint fluid viscosity. Evaluations were carried out for 6 weeks from treatment.

b. Results

Clinical and laboratory parameters which provided the most meaningful evaluation of dose groups were: lameness, range of motion, stride after exercise, cast volume, synovial fluid protein and synovial fluid viscosity.

Graphs are provided (Figures 1 through 6) to show the combined results of the data from six horses in each treatment group.

Clinical judgment of the investigator indicated that all but the placebo and 5 mg Legend Injectable Solution doses were equally effective. Judgments

were based upon clinical locomotion parameters (e.g., flexion, stride, lameness). There was evidence of consistent benefit by two weeks after initial hyaluronate sodium treatment. Maximum benefit inclusive of virtual complete alleviation of lameness appeared to occur from the fourth to sixth week. Stride, however, appeared mostly resolved by the time of the second week observation, but clinical judgment still revealed some residual lameness at this time. It was notable that swelling (based upon carpal circumference and cast volume) resolved more slowly and less completely during the overall observation period.

It was also noted that improvement in joint fluid protein values were likewise less complete. There was no significant change in viscosity. The variation of joint fluid WBC did not permit interpretation.

Figure 1: Lameness Change Over Time By Dose Group

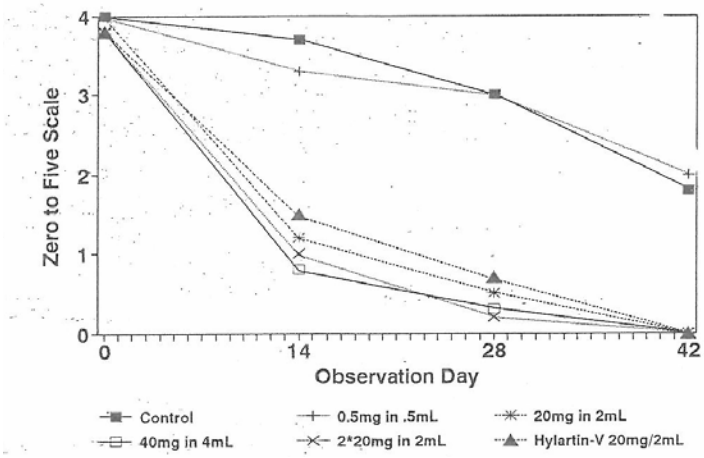


Figure 2: Carpal Joint Range of Motion Change Over Time By Dose Group

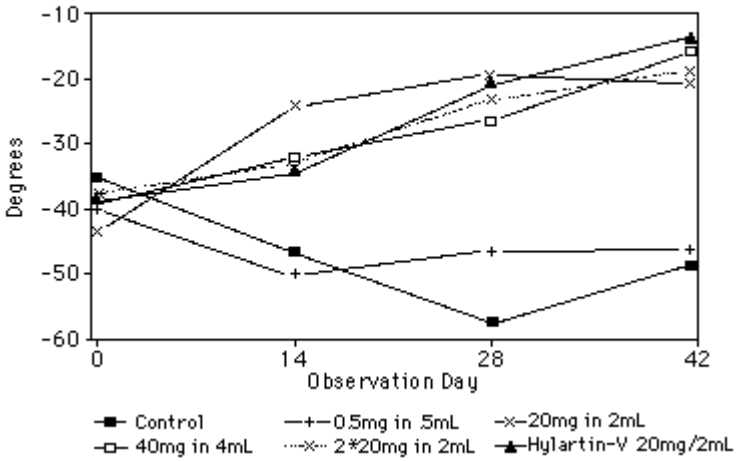


Figure 3: Stride After Exercise, Change Over Time By Dose Group

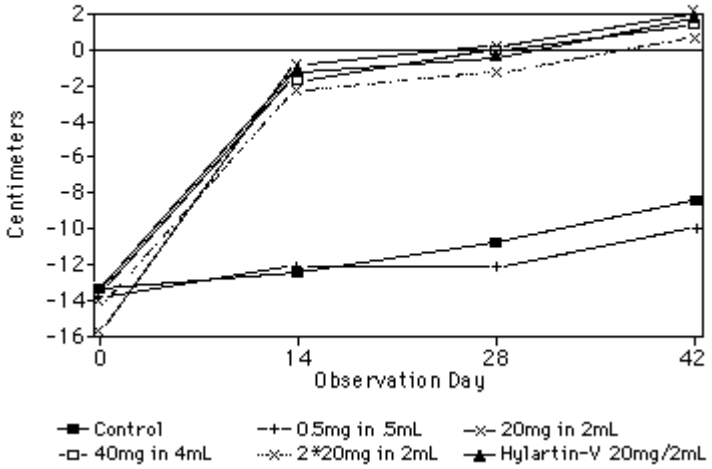


Figure 4: Cast Volume Change Over Time By Dose Group

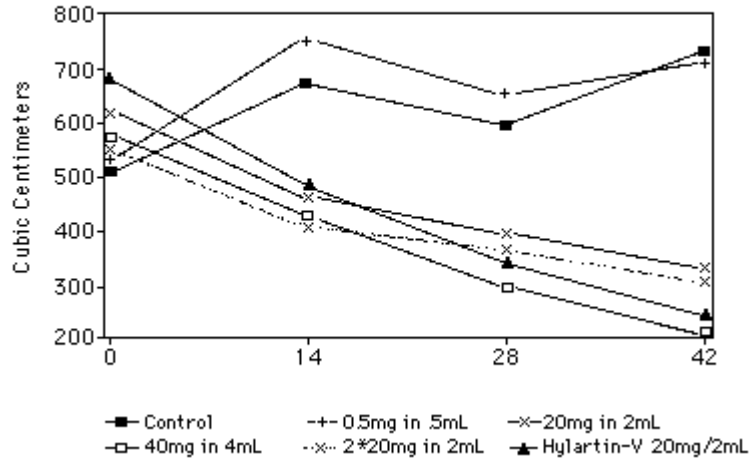


Figure 5: Carpal Joint Fluid Protein
Change Over Time By Dose Group

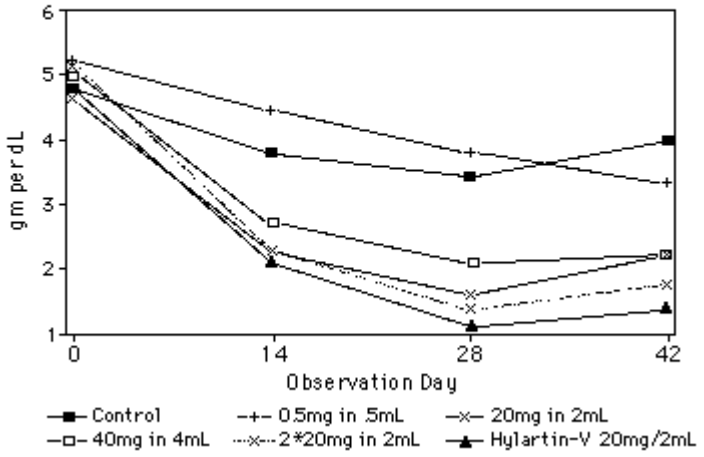
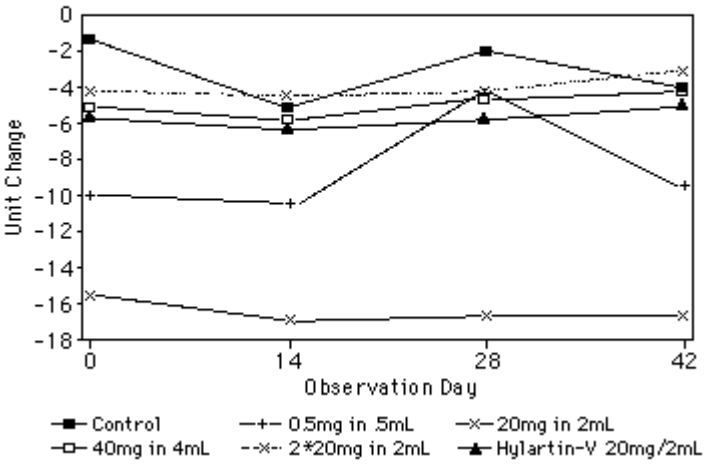


Figure 6: Relative Viscosity of Carpal Joint Fluid
Change Over Time By Dose Group



An examination of Figures 1 through 4 reveals a definite difference in response between dose groups. Figure 5 is less definite and Figure 6 shows little difference between dose groups based on this parameter.

c. Statistical Evaluation

An analysis of variance was run at each observation period for each variable. Statistical evaluation was conducted by Hamm and Walls Associates.

The lowest dose (5 mg) was not statistically significantly different from the negative control at all times and all measures. In general, the large doses (20 and 40 mg) of Legend Injectable Solution and positive control drug were statistically different ($p < 0.05$) from the negative control and 5 mg

dose groups. Thus, all but the lowest dose of hyaluronate sodium were found to be comparable in efficacy to the positive control and there was insufficient statistical evidence to establish an unequivocal preference among the higher dose treatment regimens utilized in this trial. These higher doses, as well as the positive control drug, were efficacious in that treated animals showed a definite return toward the baseline values.

The variables showing this pattern of result included: lameness, standing angle, flexed angle, range of motion, stride after rest, stride after exercise, volume of cast, circumference over carpal joint, protein and to some extent, the white blood cell count. Temperature, pulse, respiration, and relative viscosity showed no significant differences among treatment groups.

d. Adverse Reactions

The investigator reported that no adverse effects were observed in this study.

e. Conclusion

These data show that the optimum effective dose of Legend Injectable Solution for intra- articular treatment of the experimentally induced carpitis is 20 mg (2 mL). Clinical signs and joint fluid analysis were statistically analyzed and support this conclusion.

2. Dose Titration Study - Intravenous Injectable Solution.

An evaluation to determine the optimum dose of Legend Injectable Solution given intravenously to treat equine carpitis was conducted by Drs. Doyne Hamm and Danny Millar, at Research for Animal Health in Fayetteville, Arkansas. Joint fluid assays were conducted at Specialized Assays in Nashville, Tennessee.

a. Study Design

This study followed the pattern set by the intra-articular dose titration study except that horses were treated intravenously with the 1% Legend Injectable Solution or saline control. The Freund's Complete Adjuvant model was used in thirty-two horses of Quarter Horse type. The horses were divided into 4 treatment groups with 8 horses in each group. Five days after model induction, a series of three, weekly injections of Legend Injectable Solution were given to each horse. The treatment doses were: 1) Phosphate Buffered Saline, negative control (4 mL); 2) 20 mg Legend (2 mL); 3) 40 mg Legend (4 mL); and 4) 80 mg Legend (8 mL). The Test Drug was the formulation intended for market.

The study was blinded by using two veterinarians. One administered drug treatments and the other conducted the evaluations and did not know which treatment each animal received.

Evaluations were made prior to induction of carpitis and every other week for six weeks. These evaluations included body temperature, pulse rate,

respiration rate, joint circumference, lameness score, standing leg angle, flexed leg angle, range of motion, stride length, cast volume, joint fluid protein, joint fluid viscosity and joint fluid WBC.

b. Results

Clinical parameters which provided the most meaningful comparison of dose groups were: carpal joint circumference, flexed leg angle, range of motion, stride length and lameness score.

Graphs are provided (Figures 7 through 11) to show the combined results of the data from eight horses in each treatment group.

Figure 7. Mean Carpal Joint Circumference
Over Days By Dose Group

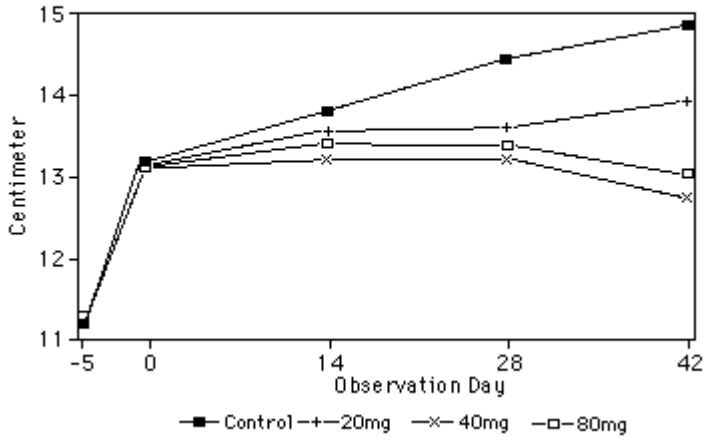


Figure 8: Mean Flexed Angle of Carpus
Over Days By Dose Group

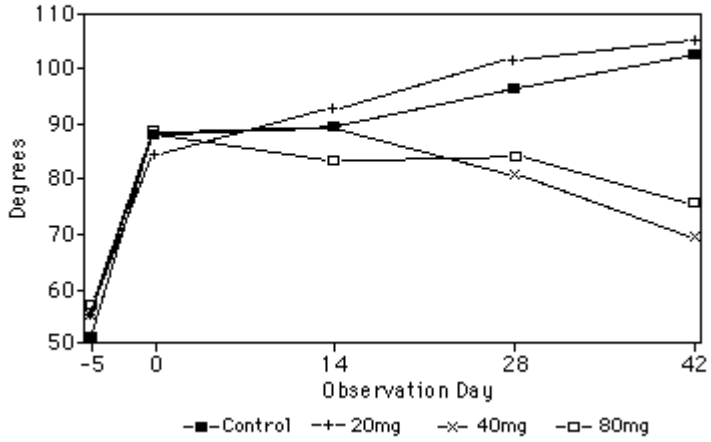


Figure 9: Carpal Joint Mean Range of Motion
Over Days By Dose Group

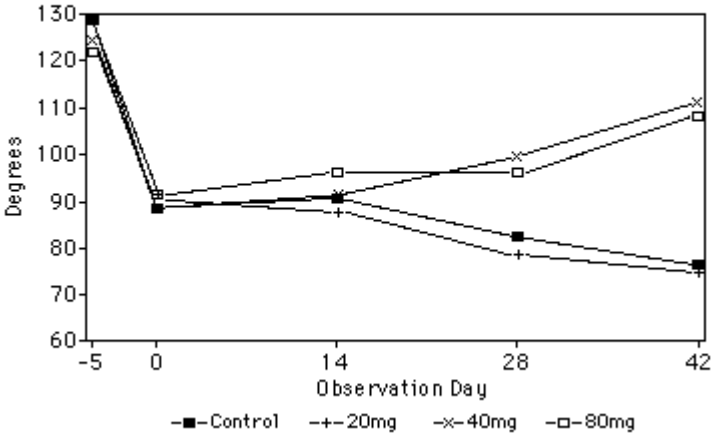


Figure 10: Mean Stride Length
Over Days By Dose Group

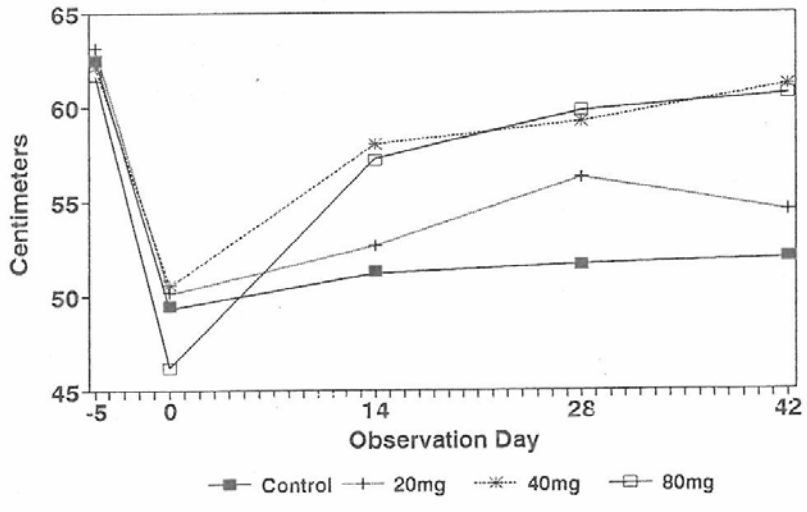
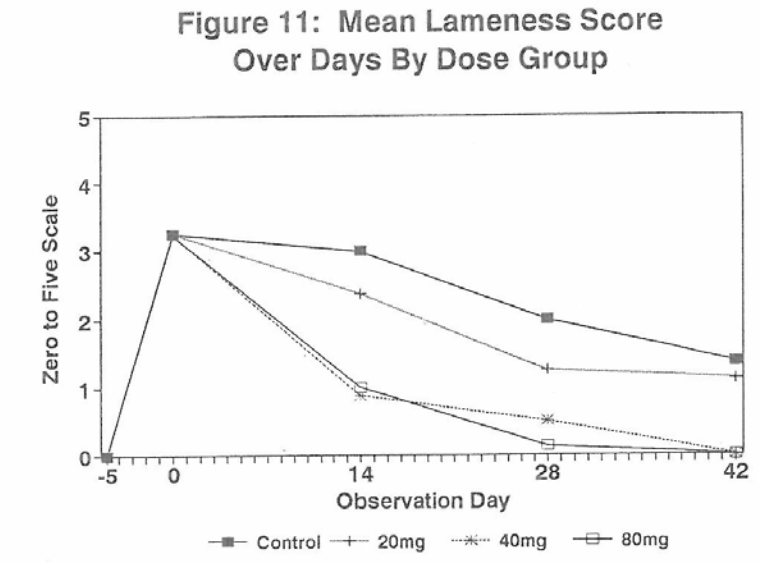


Figure 11: Mean Lameness Score Over Days By Dose Group



c. Statistical Evaluation

For each variable in the study, a separate analysis of variance was performed on each day. This analysis was followed by a Duncan's multiple range procedure (0.05 level) to contrast each pair of treatment group means. The same analyses were performed on the change from baseline data obtained by subtracting the value of Day -5 from each of the following day values on each individual horse.

Significant improvement ($p < 0.05$) was seen by the 14th day on flexed angle, range of motion, stride length and lameness score on those animals treated with 40 or 80 mg as compared to those treated at 20 mg or the Controls.

As a rule, no significant differences were seen between the low dose and the controls or between the two highest doses.

d. Adverse Reactions

The investigator reported that no adverse effects were observed in this study.

e. Conclusion

It is concluded that 40 mg of Legend Injectable Solution used intravenously is the optimal dose for the treatment of experimentally induced carpitis in the horse.

3. Clinical Trial

A well-controlled clinical trial was conducted to determine the efficacy and safety of Legend (hyaluronate sodium) Injectable Solution for the treatment of joint dysfunction in horses due to non-infectious synovitis associated with equine osteoarthritis. This trial was conducted in two phases (Phase I and Phase II) by the following principal investigators: Dr. Mike Betley, Barrington,

IL; Dr. Jerry Black, Oakdale, CA; Dr. Robert Lewis, Elgin, TX; and Dr. Doyne Hamm, Fayetteville, AR. Principal investigators for both phases were the same and the two protocols used the same critical parameters, allowing for the data to be pooled for analytical purposes. The pooled data as well as the results from each phase are presented below. The time interval between the two phases of the clinical field trial did not influence the results. Therefore, combining the results constitutes one adequate and well-controlled clinical field trial.

a. Study Design

The purpose of the clinical trial was to evaluate the efficacy and safety of Legend Injectable Solution when administered either intravenously or intra-articularly in treating horses with clinical cases of degenerative joint disease. There was no other drug approved for intravenous administration, therefore, the positive control was administered by intra- articular injection only.

Cases were selected on the basis of clinical symptoms of synovitis of a carpus or a fetlock joint including lameness, and signs of heat and pain on palpation.

The horses entered into the study were divided into three treatment groups. Breeds included Thoroughbreds, Standardbreds and Quarter Horses. Seventy-two horses successfully completed the study. Twenty-one horses were treated with 40 mg (4 mL) of Legend Injectable Solution (1% hyaluronate sodium solution) in the jugular vein. Twenty-five horses were treated with 20 mg (2 mL) of the same Test Drug by an intra-articular injection. The Test Drug was the formulation intended for market. The final twenty-six horses were treated intra-articularly with 20 mg (2 mL) of a commercial hyaluronate sodium control drug (Hylartin-V). A total of fifty-one horses with dysfunction of one carpal joint and twenty-one horses with dysfunction of one fetlock joint were treated.

Horses were treated one, two or three times, at weekly intervals based on an evaluation of the response by the investigator.

The study was blinded with one investigator at each location conducting all evaluations (without knowing which treatments were given) while a second administered all treatments. In addition, the three treatment groups were randomly assigned. Evaluations were conducted as follows:

Lameness was scored on a scale of 0 to 5, with 0 meaning no lameness and 5 meaning refusal to move.

Pain on Palpation was scored on a scale of 0 to 3, with 0 meaning no pain reaction and 3 meaning that palpation was not possible.

Heat was scored from 0 to 3 with 0 meaning a normal joint and 3 meaning the joint was hot to the touch.

Overall Response Rating was scored after the horse was back in training and was rated as Excellent, Good, Fair or None.

Joint Fluid samples were taken at the time of each treatment and evaluated for: Protein, Hyaluronic Acid Concentration, Viscosity, WBC and Mucin Clot.

b. Pooled Results

A summary of the clinical response results by route of administration is shown in Table 1. Tables 2 and 3 show the clinical response by joint. The overall response ratings are shown in Table 4, with Tables 5 and 6 providing the results by joint treated.

Table 1. Analysis of Clinical Response by Route of Administration

Parameter	Treatment	n	Pre	Post	Difference*
Lameness	Legend IV	21	2.8	0.8	-2.0
Lameness	Legend IA	25	2.8	0.7	-2.1
Lameness	Control IA	26	3.0	1.2	-1.8
Pain	Legend IV	21	2.2	0.7	-1.5
Pain	Legend IA	25	2.3	0.6	-1.8
Pain	Control IA	26	2.3	1.0	-1.4
Heat	Legend IV	21	1.5	0.5	-1.1
Heat	Legend IA	25	1.6	0.3	-1.3
Heat	Control IA	26	1.6	0.4	-1.2

* Actual differences may be slightly different than what is shown due to rounding

Table 2. Analysis of Clinical Response by Route of Administration - Carpus Only

Parameter	Treatment	n	Pre	Post	Difference*
Lameness	Legend IV	15	2.7	0.8	-1.9
Lameness	Legend IA	17	2.8	0.7	-2.1
Lameness	Control IA	19	3.0	1.0	-2.1
Pain	Legend IV	15	2.3	0.7	-1.6
Pain	Legend IA	17	2.3	0.5	-1.8
Pain	Control IA	19	2.3	1.0	-1.4
Heat	Legend IV	15	1.7	0.6	-1.1
Heat	Legend IA	17	1.8	0.4	-1.4
Heat	Control IA	19	1.7	0.4	-1.3

* Actual differences may be slightly different than what is shown due to rounding

Table 3. Analysis of Clinical Response by Route of Administration - Fetlock Only

Parameter	Treatment	n	Pre	Post	Difference*
Lameness	Legend IV	6	3.0	0.8	-2.3
Lameness	Legend IA	8	2.8	0.8	-2.0
Lameness	Control IA	7	3.0	1.6	-1.4
Pain	Legend IV	6	2.0	0.6	-1.5
Pain	Legend IA	8	2.4	0.8	-1.6

Parameter	Treatment	n	Pre	Post	Difference*
Pain	Control IA	7	2.4	0.9	-1.5
Heat	Legend IV	6	1.2	0.0	-1.2
Heat	Legend IA	8	1.3	0.1	-1.2
Heat	Control IA	7	1.4	0.3	-1.1

* Actual differences may be slightly different than what is shown due to rounding

Table 4. Overall Response Rating by Route of Administration

	Excellent/Good n (%)	Fair n	None n	Total
Legend IV	19 (90)	1	1	21
Legend IA	24 (96)	0	1	25
Control IA	23 (88)	2	1	26
Total	46	3	3	72

Table 5. Overall Response Rating by Route of Administration - Carpus Only

	Excellent/Good n (%)	Fair n	None n	Total
Legend IV	13 (87)	1	1	15
Legend IA	16 (94)	0	1	17
Control IA	17 (89)	1	1	19
Total	46	2	3	51

Table 6. Overall Response Rating by Route of Administration - Fetlock Only

	Excellent/Good n (%)	Fair n	None n	Total
Legend IV	6 (100)	0	0	6
Legend IA	8 (100)	0	0	8
Control IA	6 (86)	1	0	7
Total	20	1	0	21

c. Statistical Methodology and Analysis of the Pooled Data

To demonstrate efficacy, McNemar's test was used comparing improvement versus worsening of condition of post-treatment response for heat, lameness and pain, combining the response data for all investigators.

The Cochran-Mantel-Haenszel categorical data analysis (row means score) procedure, controlling for investigator, was used to test for pre- and post-treatment differences among treatment groups for heat, lameness and pain. For each response variable an overall analysis, combining fetlock and carpus cases and separate joint analyses were investigated. The same method was used to analyze the overall rating.

As supportive analysis, post-treatment responses were analyzed in a blocked one-way analysis of variance incorporating study investigator, treatment and treatment by investigator terms. The study investigator and treatment by investigator terms were considered as random effects. A 90%

confidence interval of treatment differences was constructed. For each response variable, an overall analysis, combining carpus and fetlock cases, and by-joint analyses were considered.

No statistical analyses were conducted for pre vs post-treatment WBC, protein and viscosity because of the lack of completed paired data.

A 0.05 level was used to determine all statistical significance.

Analysis of clinical response data showed that IV treatment was as effective as IA with either the Test or Control Drug (Table 1). All indicated a significant improvement in response ($p <= 0.05$). There was no statistically significant difference between treatment groups for any of the parameters measured pre-treatment. The combined data for Overall Response Rating are shown in Table 4. The table reveals that most horses responded with an excellent or good rating. The results of statistical analysis showed no consistent differences among the treatment groups.

d. Conclusion

The results of this adequate and well-controlled clinical trial from 4 investigator sites using 72 horses demonstrated a clinically significant reduction in lameness. Most of the horses treated either intravenously or intra-articularly with Legend Injectable Solution returned to work, training or racing without recurrence of symptoms during the observation period.

No adverse reactions were observed in any of the treated horses, demonstrating safety for both routes of administration.

3.1. Clinical Trial – Phase I

Thirty-seven horses were divided into three treatment groups. Breeds included Thoroughbreds, Standardbreds and Quarter Horses. Eleven horses were treated with 40 mg (4 mL) of Legend Injectable Solution (1% hyaluronate sodium solution) in the jugular vein. Twelve horses were treated with 20 mg (2 mL) of the same Test Drug by an intra-articular injection. The Test Drug was the formulation intended for market. The final 14 horses were treated intra-articularly with 20 mg (2 mL) of a commercial hyaluronate sodium Control drug (Hylartin-V). A total of 24 carpal joints and 13 fetlock joints were treated.

A summary of the clinical response is shown in Tables 7-9. Table 7 shows combined results for both the carpal and fetlock joints while Tables 8 and 9 separate the results by joint.

Table 7. Analysis of Clinical Response by Route of Administration

Parameter	Treatment	n	Pre	Post	Difference*
Lameness	Legend IV	11	3.0	1.4	-1.7
Lameness	Legend IA	12	2.8	0.8	-2.0
Lameness	Control IA	14	3.1	1.4	-1.7
Pain	Legend IV	11	2.0	0.5	-1.5
Pain	Legend IA	12	2.2	0.6	-1.6

Parameter	Treatment	n	Pre	Post	Difference*
Pain	Control IA	14	2.1	0.9	-1.1
Heat	Legend IV	11	1.3	0.4	-0.9
Heat	Legend IA	12	1.4	0.2	-1.3
Heat	Control IA	14	1.6	0.4	-1.3

* Actual differences may be slightly different than what is shown due to rounding

Table 8. Analysis of Clinical Response by Route of Administration - Carpus Only

Parameter	Treatment	n	Pre	Post	Difference*
Lameness	Legend IV	7	3.0	1.4	-1.7
Lameness	Legend IA	7	3.0	0.7	-2.3
Lameness	Control IA	10	3.2	1.2	-2.0
Pain	Legend IV	7	2.0	0.7	-1.3
Pain	Legend IA	7	2.0	0.6	-1.4
Pain	Control IA	10	2.0	0.8	-1.2
Heat	Legend IV	7	1.3	0.6	-0.7
Heat	Legend IA	7	1.6	0.1	-1.5
Heat	Control IA	10	1.6	0.4	-1.2

* Actual differences may be slightly different than what is shown due to rounding

Table 9. Analysis of Clinical Response by Route of Administration - Fetlock Only

Parameter	Treatment	n	Pre	Post	Difference*
Lameness	Legend IV	4	3.0	0.8	-2.2
Lameness	Legend IA	5	2.6	1.0	-1.7
Lameness	Control IA	4	2.8	1.5	-1.3
Pain	Legend IV	4	2.0	0.0	-2.0
Pain	Legend IA	5	2.4	0.6	-1.8
Pain	Control IA	4	2.3	1.0	-1.3
Heat	Legend IV	4	1.3	0.0	-1.3
Heat	Legend IA	5	1.2	0.2	-1.0
Heat	Control IA	4	1.8	0.3	-1.5

* Actual differences may be slightly different than what is shown due to rounding

Joint fluid analysis was carried out on samples taken at the first and last treatment. Results are shown in Table 10. An improvement in chemistry profile indicates a relative improvement in joint function. This is best shown with viscosity, hyaluronic acid concentration, protein and white blood cell count.

Table 10. Analysis of Joint Fluid Chemistry

Parameter	Treatment	Pre	n	Post	n	Difference*
Viscosity	Legend IV	4.9	9	9.0	7	+4.0
Viscosity	Legend IA	8.1	12	7.1	6	-1.0
Viscosity	Control IA	7.6	10	4.2	10	-3.4

Parameter	Treatment	Pre	n	Post	n	Difference*
H.A. Concentration	Legend IV	1.7	9	2.4	7	+0.7
H.A. Concentration	Legend IA	2.4	12	2.3	7	-0.1
H.A. Concentration	Control IA	2.6	10	2.1	11	-0.5
Protein	Legend IV	2.1	9	2.3	7	+0.1
Protein	Legend IA	1.8	12	1.4	8	-0.3
Protein	Control IA	1.8	10	1.9	11	+0.2
WBC	Legend IV	319.7	9	1749.1	7	+1429.4
WBC	Legend IA	612.9	12	69.0	8	-543.9
WBC	Control IA	120.7	10	255.6	11	+135.2

* Actual differences may be slightly different than what is shown due to rounding

The final Overall Response Rating is shown in Tables 11-13. The tables show that most horses responded with an excellent or good rating. Table 11 shows combined results of both carpal and fetlock joints. Tables 12 and 13 further break down the results by joint treated.

Table 11. Overall Response Rating by Route of Administration

	Excellent/Good	Fair	None
Legend IV	9	1	1
Legend IA	12	0	0
Control IA	11	2	1

Table 12. Overall Response Rating by Route of Administration – Carpus Only

	Excellent/Good	Fair	None
Legend IV	5	1	1
Legend IA	7	0	0
Control IA	8	1	1

Table 13. Overall Response Rating by Route of Administration – Fetlock Only

	Excellent/Good	Fair	None
Legend IV	4	0	0
Legend IA	5	0	0
Control IA	3	1	0

3.2. Clinical Trial – Phase II

Thirty-five horses were treated including Quarter Horses, Standardbreds and Thoroughbreds. Ten received 40 mg (4 mL) of Legend Injectable Solution (1% hyaluronate sodium) in the jugular vein. Thirteen horses were treated with 20 mg (2 mL) of the same Test Drug by an intra-articular injection. The Test Drug formulation was the formulation intended for market. The final twelve horses were treated intra-articularly with 20 mg (2 mL) of a commercial hyaluronate sodium Control drug (Hylartin-V). A total of 27 carpal joints and 8 fetlock joints were treated.

A summary of the clinical response is shown in Tables 14-16. Table 14 shows combined results for carpal and fetlock joints, while Tables 15 and 16 show the results by joint.

Table 14. Analysis of Clinical Response by Route of Administration

Parameter	Treatment	n	Pre	Post	Difference*
Lameness	Legend IV	10	2.5	0.30	-2.20
Lameness	Legend IA	13	2.77	0.62	-2.15
Lameness	Control IA	12	2.83	0.92	-1.92
Pain	Legend IV	10	2.40	0.80	-1.60
Pain	Legend IA	13	2.46	0.54	-1.92
Pain	Control IA	12	2.58	1.00	-1.58
Heat	Legend IV	10	1.80	0.50	-1.30
Heat	Legend IA	13	1.77	0.46	-1.31
Heat	Control IA	12	1.58	0.42	-1.17

* Actual differences may be slightly different than what is shown due to rounding

Table 15. Analysis of Clinical Response by Route of Administration – Carpus Only

Parameter	Treatment	n	Pre	Post	Difference*
Lameness	Legend IV	8	2.40	0.25	-2.15
Lameness	Legend IA	10	2.70	0.70	-2.00
Lameness	Control IA	9	2.67	0.67	-2.00
Pain	Legend IV	8	2.50	0.63	-1.87
Pain	Legend IA	10	2.50	0.40	-2.10
Pain	Control IA	9	2.56	1.11	-1.45
Heat	Legend IV	8	2.00	0.63	-1.37
Heat	Legend IA	10	1.90	0.60	-1.30
Heat	Control IA	9	1.78	0.44	-1.34

* Actual differences may be slightly different than what is shown due to rounding

Table 16. Analysis of Clinical Response by Route of Administration – Fetlock Only

Parameter	Treatment	n	Pre	Post	Difference*
Lameness	Legend IV	2	3.00	0.50	-2.50
Lameness	Legend IA	3	3.00	0.33	-2.67
Lameness	Control IA	3	3.33	1.67	-1.66
Pain	Legend IV	2	2.00	1.50	-0.50
Pain	Legend IA	3	2.33	1.00	-1.33
Pain	Control IA	3	2.67	0.67	-1.00
Heat	Legend IV	2	1.00	0.00	-1.00
Heat	Legend IA	3	1.33	0.00	-1.33
Heat	Control IA	3	1.00	0.33	-0.67

* Actual differences may be slightly different than what is shown due to rounding

Joint Fluid Analysis was carried out on samples taken at the first and last treatment. Results are shown in Table 17.

Table 17. Analysis of Joint Fluid Chemistry

Parameter	Treatment	Pre	n	Post	n	Difference*
Viscosity	Legend IV	3.38	5	3.94	7	+0.56
Viscosity	Legend IA	3.03	8	3.83	9	+0.81
Viscosity	Control IA	4.56	7	3.33	6	-1.22
Protein	Legend IV	1.73	9	1.81	7	+0.08
Protein	Legend IA	1.75	12	1.77	11	+0.02
Protein	Control IA	2.18	11	2.12	10	-0.06
WBC	Legend IV	473.33	9	337.14	7	-136.19
WBC	Legend IA	336.67	12	512.73	11	+176.06
WBC	Control IA	704.55	11	696.00	10	-8.55

* Actual differences may be slightly different than what is shown due to rounding

The final Overall Response Rating is shown in Tables 18-20. The tables reveal that except for one case, all horses in all groups responded with an Excellent or Good rating. Table 18 shows combined results for both carpal and fetlock joints. Tables 19 and 20 further break down the data by joint treated.

Table 18. Overall Response Rating by Route of Administration

	Excellent/Good	Fair	None
Legend IV	10	0	0
Legend IA	12	0	1
Control IA	12	0	0

Table 19. Overall Response Rating by Route of Administration – Carpus Only

	Excellent/Good	Fair	None
Legend IV	8	0	0
Legend IA	9	0	1
Control IA	9	0	0

Table 20. Overall Response Rating by Route of Administration – Fetlock Only

	Excellent/Good	Fair	None
Legend IV	2	0	0
Legend IA	3	0	0
Control IA	3	0	0

B. Corroborative Study.

1. Clinical Trial - Intra-articular Injectable Solution

The objective of this clinical trial was to evaluate the results in horses treated with 20 mg (2 mL) of Legend Injectable Solution. Four investigators at different geographical sites were selected. These were Dr. M. J. Betley,

Chicago, IL; Dr. J. Black, Oakdale, CA; Dr. B.Wm. Furlong; Oldwick, NJ; and Dr. D. Hamm, Fayetteville AR.

a. Study Design

Eighty-two cases of joint dysfunction of the equine carpus were studied. Forty cases were randomly selected for treatment with the Legend Injectable Solution Test Drug and forty- two with a commercially available 1% hyaluronate sodium positive Control Drug. The Test Drug formulation was the one intended for market. Both drugs were injected intra-articularly into the carpus at the rate of 20 mg (2 mL) per dose. Repeat treatments at weekly intervals were allowed to a total of three injections.

Horses were evaluated for lameness, joint pain, effusion, range of motion and overall improvement.

b. Results

Improvements were noted in joint condition of horses treated with both drugs. The Overall Response Rating for both products was essentially equal.

c. Adverse Reaction

No adverse reactions were reported by investigators using the Test or Control drug in these studies.

d. Conclusion

The results of this clinical trial conducted at four locations indicate that Legend Injectable Solution given by intra-articular injection is beneficial in the treatment of noninfectious synovitis associated with osteoarthritis in the equine carpus. A dose of 20 mg (2 mL) compared favorably to a commercially available hyaluronate sodium product when evaluating joint dysfunction parameters by laboratory examination of synovial fluid.

2. Clinical Trial - Intravenous Injectable Solution

A clinical trial was conducted at two locations to provide an early evaluation of intravenous treatment of natural clinical cases. Studies were conducted by Dr. Michael J. Betley in Chicago, Illinois, from September to December, 1986 and by Dr. Doyne Hamm, at Fayetteville, Arkansas, from March to May, 1987.

a. Study Design

A total of 41 horses were treated from the two sites in a non-controlled study. This early investigation was conducted to evaluate this route of administration under field conditions using natural cases of joint dysfunction of the carpus. Both investigators treated Thoroughbred or Quarter Horses which were in training at local stables or tracks.

All horses were treated intravenously with a 1% solution of hyaluronate sodium using a dose of 40 mg (4 mL). The Test Drug was the formulation intended for market. Selection for treatment was based on clinical

observations of lameness, joint pain, effusion and flexion. Repeat treatments for a total of three weekly injections were allowed. Joint fluid samples were analyzed for synovial protein, viscosity and WBC count.

b. Results

Results indicated a favorable response with all horses improving in the clinical parameters. Joint fluid analysis indicated a general trend toward improvement in protein and viscosity measurements.

c. Adverse Reactions

There were no adverse reactions reported by either investigator.

d. Conclusion

This study indicated that 40 mg Legend Injectable Solution, injected intravenously, resulted in improvement of equine degenerative joint disease of the carpus. Additional controlled studies were indicated.

III. ANIMAL SAFETY

A. Pivotal Studies

Three pivotal safety studies for the intra-articular and intravenous use of Legend Injectable Solution in horses were conducted as per Good Laboratory Practice Regulations.

1. Safety Evaluation for the Intra-Articular Use of Hyaluronate Sodium in Horses

M. Kohlenberg of Shawnee Mission, Kansas used 16 Quarter Horse type, adult male and female horses in a general target species safety conducted with the Legend Injectable Solution formulation via intra-articular treatment. Each of 4 groups contained 4 horses with treatments injected into the right intercarpal joint. Group I horses received 2 mL of sterile saline, Group II horses received 2 mL of Legend Injectable Solution (use rate), Group III horses received 6 mL of Legend Injectable Solution (3X use rate) and Group IV horses received 10 mL of Legend Injectable Solution (5X use rate). Each horse received 9 treatments at 7 day intervals (3X the labeled duration). The Legend Injectable Solution was the formulation intended for market. The purpose of the study was to determine a margin of safety for the intra-articular administration of Hyaluronate 1% Injectable to horses.

Parameters monitored included clinical signs, body weights, joint swellings, body temperatures, hematology parameters (white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, prothrombin time, WBC differential, RBC morphology and platelet count), serum chemistries (calcium, phosphorus, glucose, blood urea nitrogen, uric acid, cholesterol, creatinine, total protein, albumin, globulin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvate transaminase, sodium, potassium, chloride; total, direct and indirect bilirubin; carbon dioxide, creatine kinase, lactic dehydrogenase, gamma-

glutamyl transpeptidase, albumin/globulin ratio, calcium/phosphorus ratio, BUN/creatinine ratio, sodium/potassium ratio, amylase and sorbitol dehydrogenase), necropsy observations and histological findings. The study was blinded for clinical chemistry and hematology as these values were collected without advising the laboratory personnel of the treatments.

All the horses gained body weight during the study. No significant post-treatment changes occurred in the body temperatures. No treatment related clinical signs were observed. Slight and mild swellings of injected joints were noted on occasions in horses within all treated groups and the saline treated control group. None of the joint swellings were classified as moderate or severe. No clinically significant trends occurred in the clinical chemistry or hematology parameter group means. No significant lesions were observed at necropsy. All soft tissues (liver, kidney, gonad, adrenal gland, urinary bladder, spleen, stomach, small intestine, colon, cecum, pancreas, lung, heart, thyroid gland, cerebrum, cerebellum, medulla and pituitary) were normal histologically as were the cartilages from the treated carpal joints.

A brief summary is presented in Table 21.

Table 21. General Safety Evaluation for Intra-Articular Use of Hyaluronate Sodium in Horses

Formulation	No. of Horses	Treatment Rate	Total Treatments
Physiological Saline	4	2 mL	9
1% Injectable	4	2 mL	9
1% Injectable	4	6 mL	9
1% Injectable	4	10 mL	9

Results Summary: No treatment related clinical signs or trends in pathology parameters occurred in any of the 4 groups. The high treatment group was evaluated for histological lesions and none were found.

This study concluded adequate safety for intra-articular treatment in horses with a 1% Legend Injectable Solution formulation. This conclusion was based upon no significant adverse effects following treatment with 5 times the labeled use rate at 7 day intervals for a total of 9 treatments.

2. Drug Tolerance Evaluation for the Intravenous Treatment of Horses with Hyaluronate Sodium

M. Kohlenberg of Shawnee Mission, Kansas conducted a drug tolerance study to evaluate the effects of excessive overdoses of hyaluronate sodium when administered intravenously for 3 consecutive days. Three adult horses (male and female) of various breeds were used in this study. Two horses received intravenous Legend Injectable Solution treatment for 3 consecutive days; one at 10 times the use rate (40 mL) and one at 25 times the use rate (100 mL). The third horse served as a control and received physiological saline treatment. The Legend Injectable Solution was the 1% formulation intended for market.

Parameters monitored included clinical signs, body weights, body temperatures, hematology parameters (white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, WBC differential, RBC morphology and platelet count), serum chemistries (sodium, potassium, chloride, glucose, blood urea nitrogen, uric acid, creatinine, BUN/Cr ratio, creatine kinase; total, direct and indirect bilirubin; alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl transpeptidase, serum glutamic pyruvate transaminase, serum glutamic oxaloacetic transaminase, total protein, albumin, globulin, A/G ratio, calcium, phosphorus, cholesterol, Ca/PO ratio, Na/K ratio and carbon dioxide), necropsy observations and histological (liver, kidney, gonad, adrenal gland, urinary bladder, spleen, stomach, small intestine, colon, cecum, pancreas, mesenteric lymph node, lung, heart, thyroid gland, cerebrum, cerebellum, medulla and pituitary) readings.

There were no clinical signs of toxicosis nor clinically significant variations in body weights or temperatures. No trends developed in the hematology or serum chemistry parameters. No significant lesions were observed at necropsy or upon histology readings. The hematology and clinical chemistry evaluations were blinded in that the laboratory personnel were unaware of the treatments given. A brief summary is presented in Table 22.

Table 22. Drug Tolerance Evaluation for the Intravenous Treatment of Horses with Hyaluronate Sodium

Formulation	No. of Horses	Treatment Rate	Total Treatments
Physiological Saline	1	100 mL	3
1% Injectable	1	40 mL	3
1% Injectable	1	100 mL	3

Results Summary: No adverse effects in any parameters for the 3 horses.

This study concluded that intravenous administration of Legend Injectable Solution at 25 times the use rate for 3 consecutive days (100 mL/day) is without adverse effects in horses.

3. Safety Evaluation for the Intravenous Use of Hyaluronate Sodium in Horses

M. Kohlenberg of Shawnee Mission, Kansas used 16 male and female horses of various breeds and with an age range of 2 to 10 years in a general target species safety evaluation to determine a margin of safety for the intravenous administration of Hyaluronate Sodium 1% Injectable to horses. Four horses served as controls and received 20 mL physiological saline treatment. Each of the remaining 3 groups contained 4 horses and they received Legend Injectable Solution intravenous treatments weekly via the jugular vein for 9 consecutive weeks which is 3 times the labeled duration. Treatment rates each week were at intravenous use rate (4 mL), 3X use rate (12 mL) or 5X use rate (20 mL). The Legend Injectable Solution was the formulation intended for market (10 mg/mL).

Parameters monitored included clinical signs, body weights, body temperatures, hematology (white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, prothrombin time, WBC differential and RBC morphology), clinical chemistries (sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, uric acid, creatinine, BUN/Cr ratio, creatine kinase; total, direct and indirect bilirubin; alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl transpeptidase, serum glutamic pyruvate transaminase, serum glutamic oxaloacetic transaminase, total protein, albumin, globulin, A/G ratio, calcium, phosphorus, cholesterol, amylase, Ca/PO ratio, Na/K ratio and sorbitol dehydrogenase), necropsy of the horses receiving 5X treatments and histological readings (liver, kidney, gonad, adrenal gland, urinary bladder, spleen, stomach, small intestine, colon, cecum, pancreas, mesenteric lymph node, lung, heart, thyroid gland, cerebrum, cerebellum, medulla, pituitary gland and the carpal joint).

No clinical signs occurred and body temperatures remained stable. Body weights were not affected. No clinically significant changes occurred in the hematology or clinical chemistry parameters. No meaningful lesions were observed at necropsy and histology evaluations showed no evidence of any drug-induced lesions in any of the soft tissues or carpal joints. The study was blinded in that the hematology and serum chemistry values were collected without advising laboratory personnel of the treatments. A brief summary is presented in Table 23.

Table 23. Safety Evaluation for the Intravenous Use of Hyaluronate Sodium

Formulation	No. of Horses	Treatment Rate	Total Treatments
Physiological Saline	4	20 mL	9
1% Injectable	4	4 mL	9
1% Injectable	4	12 mL	9
1% Injectable	4	20 mL	9

Results Summary: No treatment related clinical signs or trends in pathology parameters occurred in any of the 4 groups. The high treatment group was evaluated for histological lesions and none were found.

This study concluded that intravenous treatment of horses is without adverse effects at dosages up to and including 20 mL/treatment (5X the use rate) when administered at 7 day intervals for a total of 9 treatments (3X the use duration).

B. Corroborative Studies

The following safety studies are supportive of the pivotal studies conducted in horses.

1. Preliminary Safety Evaluation for Intravenous, Intramuscular and Subcutaneous Treatment of Horses

M. Kohlenberg of Shawnee Mission, Kansas used 6 adult male and female horses of various breeds in an uncontrolled preliminary safety study with the Legend Injectable Solution intended for market. Two received intravenous treatments of 2 mL for two consecutive days and a third treatment after a 2 week interval. Likewise, two received intramuscular injections and two were treated subcutaneously with 2 mL of product according to the same schedule.

Parameters were pain response, tissue swelling and clinical signs, including those of sensitization.

No adverse effects were observed.

2. Preliminary Safety Evaluation for Intravenous Administration to Horses

T. Wollen of Shawnee Mission, Kansas used 6 mixed-breed male and female horses with an age range of 2 to 10 years in a preliminary uncontrolled safety evaluation for intravenous use of Legend 1% Injectable Solution. Five horses received three 4 mL intravenous treatments at weekly intervals. One additional horse received the same treatment schedule, but the product was injected perivascularly.

Parameters were clinical signs, body temperatures and observations for swelling or pain at the site of injection.

No side effects were observed in this study utilizing the intravenous route of administration. It furthered corroborated that perivascular treatment did not induce adverse effects.

3. Additional Safety Evaluation for Intravenous Administration to Horses; Including a Determination for Sensitization Potential

M. Kohlenberg of Shawnee Mission, Kansas used 6 male and female adult horses of Quarter Horse type in an additional uncontrolled preliminary safety study to evaluate intravenous treatment. Three horses received 3 treatments on alternate days and a fourth treatment 16 days later at a rate of 4 mL per treatment. Three additional horses were treated via the same schedule but the dosage rate was 8 mL per treatment.

Parameters were clinical signs (including observations for any potential sensitization), body temperatures, body weights and local tolerance at the injection site.

There were no side effects and the study further corroborated the safety of intravenous treatment of horses with Legend Injectable Solution.

4. Clinical Field Trial Safety Studies

Confirmation of safety for the intra-articular and intravenous treatment of horses with Legend Injectable Solution was achieved in the clinical field trials.

No adverse local or systemic side effects were observed in the horses treated with Legend Injectable Solution in any of the clinical field trials. See sections 4.A. and 4.B. of this FOI Summary.

In conclusion, the clinical field trials substantiate an adequate safety margin for the intra- articular treatment of the carpal or fetlock joint in horses with a dose of 20 mg (2 mL) per treatment of Legend Injectable Solution for 3 treatments at weekly intervals. The trials further verify the safety for the intravenous use of Legend Injectable Solution for 3 treatments at weekly intervals with a dose of 40 mg (4 mL) per treatment.

IV. HUMAN SAFETY

A. Human Food Safety

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

B. Human Safety Relative to Possession, Handling and Administration

Hyaluronate Sodium is a naturally occurring substance in both man and animals. As such, there are no special handling requirements for the drug. As a prescription drug, there are adequate directions in the labeling for the proper use of Legend Injectable Solution by the veterinarian.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data in the NADA demonstrate that Legend (hyaluronate sodium 10 mg/mL) Injectable Solution is safe and effective when used in accordance with the labeling directions.

Under Section 512(c)(2)(F)(ii) of the Federal Food, Drug and Cosmetic Act, this new animal drug application qualifies for a period of 3 years of marketing exclusivity. The active ingredient in Legend (hyaluronate sodium) has previously been approved in another NADA, NADA 112-048 for the use of hyaluronate sodium for intra-articular administration in horses for the treatment of joint dysfunction of the carpus and fetlock due to non- infectious synovitis associated with equine osteoarthritis. New clinical or field investigations (other than bioequivalence studies) were essential for approval of this NADA for the intravenous route of administration and were conducted or sponsored by the applicant.

The safe and effective use of Legend (hyaluronate sodium) Injected intra-articularly or intravenously in horses requires a veterinarian's knowledge of aseptic technique and knowledge of the anatomy of the specific joint. Therefore, the Agency has concluded that this drug product must be provided to the public on a prescription basis.

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.