

I. GENERAL INFORMATION

A. File Number

NADA 140-474

B. Sponsor

Sterivet Laboratories Limited
3909 Nashua Drive
Mississauga, Ontario
Canada

C. Proprietary Name

Synacid™

D. Established Name

hyaluronate sodium

E. Dosage and Administration

Synacid is supplied in single dose vials containing 5 ml (50 mg) of a 10 mg/ml sterile solution of hyaluronate sodium, with 0.450 mg/ml sodium benzoate, 0.096 mg/ml methylparaben and mg/ml propylparaben as preservatives.

The recommended dose is 5 ml (50 mg) of Synacid given intra-articularly in carpal and fetlock joints. Synacid should be injected under strict aseptic conditions and effusion should be removed prior to injection.

F. Dispensing Status

Prescription

G. Indication

Synacid is indicated for the treatment of equine carpal and fetlock joint dysfunction caused by traumatic and/or degenerative joint disease of mild to moderate severity.

II. EFFECTIVENESS

A. The effectiveness of Synacid has been demonstrated in the three pivotal studies which are summarized below.

1. Dose Response Study

The purpose of the study was to determine the optimal therapeutic dose of Synacid.

The dose response study was conducted by Drs. Doyne Harem and Gary Frances of Research for Animal Health Inc., Fayetteville, Arkansas. Dr. Wynn E. Jones of Mississippi State University served as the quality control director of the study. The study was conducted on a double-blind basis, with Dr. Frances administering treatments and Dr. Hamm performing the evaluations.

An adjuvant carpal model was used to assess the efficacy of four different doses of Synacid (5, 20, 50, and 75 mg) and of two control treatments (saline placebo and a positive active drug control). The positive control was administered at its recommended therapeutic dose.

The arthritic model was induced with a single intra-articular injection of 0.5 ml Freund's Adjuvant into the radiocarpal joint using standard aseptic technique. This carpal model is characterized by:

1. Inflammation of the synovial membrane, exudation into the joint cavity, tenderness and peri-arthritis, and is therefore compatible with the intended use of Synacid.
2. A syndrome which is uniform and persistent for the duration of the study, permitting practical group sizes.
3. Parameters which lend themselves to quantitative evaluation of the treatment response (joint circumference, stride length, and angle of flexion).
4. Characteristics which provide for confirmation of the syndrome (e.g. joint fluid).

Thirty-six healthy mature horses of Quarterhorse type served as the experimental animals. There were 17 geldings, 18 mares and 1 stallion, ranging in age from 2 to 6 years and weighing from 796 lbs to 1016 lbs. Animals were acclimated to the environment over a 10 day period, maintained in covered stalls and fed a routine weight maintenance ration with hay and water ad libitum. Animals were randomly allocated to one of the six treatment groups, and the study was run in 3 replicates of 12 animals, with each treatment dosage being equally represented. Therefore six animals were tested at each dosage.

Model induction occurred following the 10 day acclimation period. A single treatment with the assigned drug dosage was administered five days after model induction.

Observations were made prior to model induction, prior to treatment and for 4 weeks post-treatment consisting of:

1. temperature, pulse and respiration (daily)
2. lameness evaluation (weekly)
 - a. angle of flexion of carpus at rest
 - b. maximum angle of flexion permitted
 - c. length of stride of lame limb after resting
 - d. length of stride of lame limb following exercise
 - e. lameness score
 - f. pain on palpation of the affected joint
 - g. hyperthermia (heat) of the affected joint
3. radiocarpal joint circumference (weekly)
4. carpal volume measurements (prior to treatment and at the conclusion of the study)
5. synovial fluid analysis of protein content (weekly)
6. hemogram (weekly)

Table 1 shows that prior to model induction, the test animals were sound and similar (normal) in their response parameters.

Table 1 DOSE RESPONSE STUDY: Means of Lameness Related Variables of the Animals in the Saline Placebo and in the 5 mg, 20 mg, 50 mg and 75 mg Synacid Dose Groups Before Model Induction

Dose Group	Flex Rest	Flex Max	Strd Rest	Strd Exer	Jt Circ	Lameness
Saline	0.00	111.67	62.33	62.83	11.58	0.00
5 mg Synacid	0.00	120.83	62.00	62.50	11.29	0.00
20 mg Synacid	0.00	120.00	62.20	62.70	11.50	0.00
50 mg Synacid	0.00	118.00	62.30	62.30	11.63	0.00
75 mg Synacid	0.00	118.00	61.50	62.00	11.42	0.00

Flex Rest flexion of carpus at rest, in degrees

Flex max maximum flexion permitted on manipulation, in degrees

Strd Rest stride length at walk after rest, in inches

Strd Exer stride length at walk after standardized exercise, in inches

Jt Circ circumference of affected radiocarpal joint, in inches

Lameness numerical score from 0 (sound) to 3 (severely lame)

The severity and uniformity of the induced arthritis model is apparent from the values in Table 2 which indicate severe lameness, (score of 3), lack of weight bearing (flexion at rest), restriction in ability to fully flex affected limb (maximum flexion permitted), decreased stride length, and increased joint circumference which reflects the presence of swelling.

Table 2 DOSE RESPONSE STUDY: Means of Lameness Related Variables of the Animals in the Saline Placebo and in the 5 mg, 20 mg, 50 mg and 75 mg Synacid Dose Groups 5 Days After Model Induction and Immediately Prior to Treatment

Dose Group	Flex Rest	Flex Max	Strd Rest	Strd Exer	Jt Circ	Lameness
Saline	11.67	55.83	46.00	44.33	13.21	3.00
5 mg Synacid	10.83	52.50	46.33	44.33	13.25	2.83
20 mg Synacid	11.67	56.67	46.00	44.00	13.17	2.83
50 mg Synacid	11.67	60.00	49.00	46.83	13.04	2.83
75 mg Synacid	11.67	59.17	50.17	48.50	12.75	3.00

Flex Rest flexion of carpus at rest, in degrees
 Flex max maximum flexion permitted on manipulation, in degrees
 Strd Rest stride length at walk after rest, in inches
 Strd Exer stride length at walk after standardized exercise, in inches
 Jt Circ circumference of affected radiocarpal joint, in inches
 Lameness numerical score from 0 (sound) to 3 (severely lame)

Statistical analyses, ignoring replicate effects, were performed to test for dose related effects for joint circumference, maximum flexion, synovial fluid protein, and lameness. A statistically significant ($p < 0.05$) dose related response was seen for circumference, flexion and lameness for 0 mg through 50 mg. There was no evidence that 75 mg gave any better results than 50 mg for these parameters. No statistically significant differences between dosage levels were seen for protein.

One week after treatment, improvement was evident in the 50 mg, 75 mg Synacid and active control treatment groups in the following response parameters:

- flexion at rest
- maximum flexion permitted
- stride length at rest and after exercise
- lameness
- hyperthermia (joint heat)
- pain on palpation
- respiration rate

Table 3 demonstrates that the improvement in lameness related variables at one week following treatment was comparable in the 50 mg and 75 mg Synacid groups. Improvement also occurred in the 20 mg Synacid group but to a lesser extent.

Table 3 DOSE RESPONSE STUDY: Means of Lameness Related Variables of the Animals in the Saline Placebo and 5 mg, 20 mg, 50 mg and 75 mg Synacid Dose Groups One Week After Treatment (day 7)

Dose Group	Flex Rest	Flex Max	Strd Rest	Strd Exer	Jt Circ	Lameness
Saline	11.67	57.50	50.50	49.17	13.38	2.83
5 mg Synacid	10.00	59.17	51.00	49.17	13.50	2.83
20 mg Synacid	10.00	61.67	51.67	50.33	13.63	2.50
50 mg Synacid	0.00	82.50	59.67	60.17	13.29	1.00
75 mg Synacid	0.00	80.00	59.83	60.83	12.92	1.00

Flex Rest flexion of carpus at rest, in degrees
 Flex max maximum flexion permitted on manipulation, in degrees
 Strd Rest stride length at walk after rest, in inches
 Strd Exer stride length at walk after standardized exercise, in inches
 Jt Circ circumference of affected radiocarpal joint, in inches
 Lameness numerical score from 0 (sound) to 3 (severely lame)

At three weeks after treatment joint circumference was reduced in the 50 mg and 75 mg Synacid groups and in the active control group, compared to the placebo, 5 mg and 20 mg Synacid groups.

A return to pre-model induction values for most lameness related variables was evident at 4 weeks in all but the 5 mg, 20 mg Synacid and placebo dosage groups. Table 4 provides the data from the 4 week post-treatment evaluation.

Table 4 DOSE RESPONSE STUDY: Means of Lameness Related Variables of the Animals in the Saline Placebo and 5 mg, 20 mg, 50 mg and 75 mg Synacid Dose Groups 4 Weeks After Treatment (day 28)

Dose Group	Flex Rest	Flex Max	Strd Rest	Strd Exer	Jt Circ	Lameness
Saline	11.67	56.67	48.00	46.33	14.13	2.67
5 mg Synacid	8.33	58.33	51.50	49.83	13.75	2.33
20 mg Synacid	6.67	63.33	53.33	53.17	13.88	2.00
50 mg Synacid	0.00	90.00	61.83	62.50	12.75	0.00
75 mg Synacid	0.00	90.83	62.00	62.67	12.79	0.17

Flex Rest flexion of carpus at rest, in degrees

Flex max maximum flexion permitted on manipulation, in degrees

Strd Rest stride length at walk after rest, in inches

Strd Exer stride length at walk after standardized exercise, in inches

Jt Circ circumference of affected radiocarpal joint, in inches

Lameness numerical score from 0 (sound) to 3 (severely lame)

A comparison of the lameness related variables in the 50 mg Synacid dose group and the active control group is provided in Table 5.

Table 5 DOSE RESPONSE STUDY: Means of Lameness Related Variables of the Animals in the 50 mg Synacid Dose Group and the Active Control Group

Evaluation	Flex Rest	Flex Max	Strd Rest	Strd Exer	Jt Circ	Lameness
Before Model Induction – 50 mg Synacid	0.00	118.00	62.30	62.30	11.63	0.00
Before Model Induction – active control	0.00	118.00	62.00	62.80	11.63	0.00
Before Treatment – 50 mg Synacid	11.67	60.00	49.00	46.83	13.04	2.83
Before Treatment – active control	10.83	60.83	49.17	47.00	13.54	3.00
One Week After Treatment – 50 mg Synacid	0.00	82.50	59.67	60.17	13.29	1.00
One Week After Treatment – active control	0.83	82.50	59.00	59.83	13.33	1.17
Four Weeks After Treatment – 50 mg Synacid	0.00	90.00	61.83	62.50	12.75	0.00
Four Weeks After Treatment – active control	0.00	83.33	61.83	62.33	13.25	0.17

Flex Rest flexion of carpus at rest, in degrees

Flex max maximum flexion permitted on manipulation, in degrees

Strd Rest stride length at walk after rest, in inches

Strd Exer stride length at walk after standardized exercise, in inches

Jt Circ circumference of affected radiocarpal joint, in inches

Lameness numerical score from 0 (sound) to 3 (severely lame)

No meaningful differences as a result of treatment with any of the six dosage groups were found for body temperature, pulse rate, white blood cell counts and red blood cell counts. The absence of change in these parameters provides evidence for the safety of all dosage levels administered.

Also, no significant differences in synovial fluid protein were found among the six dosage groups studied. In each case, including saline placebo, synovial fluid protein levels declined progressively, making it difficult to detect dose group effects.

Conclusion

The conclusion that can be drawn from this study is that 50 mg of Synacid is the optimal dosage for resolving lameness related variables. A 50 mg dose of Synacid is significantly superior to a placebo, 5 mg dose and 20 mg dose of Synacid. A 75 mg dose of Synacid does not result in more improvement than the 50 mg dose of Synacid. The positive control drug used in this experiment, was found to be clinically equivalent to the 50 mg and 75 mg Synacid doses.

2. Force Plate Clinical Efficacy Study

The therapeutic effectiveness of Synacid was investigated in 22 naturally occurring cases of equine osteoarthritis, using the Standing Force Plate as an objective and quantitative measure of lameness.

The study was conducted by Dr. Anita Aviad between September, and June, 1985 at the Sterivet Research Centre in Dundas, Ontario. Dr. David Nunamaker, Jacques Jenny Professor of Orthopedic Surgery at the University of Pennsylvania School of Veterinary Medicine evaluated the force plate system and the experimental design used in this study.

The force plate was designed by George W. Pratt, Jr. Ph.D., Professor of Electrical Engineering and Computer Science, of the Massachusetts Institute of Technology. The standing force plate measures fluctuations in weight bearing of one limb at a time. Two thousand signals are recorded in the 11 second duration of each test. Fluctuations in the ability of a leg to support weight with a constant force pressure are computed in the form of a histogram with a resultant relative standard deviation, or FPU. The lower the FPU, the sounder the limb, indicating that it can support weight evenly. The higher the FPU, the lamer the limb, indicating instability in weight bearing which is caused by pain when a sore leg is in support. Lameness is also evaluated by comparison of the FPU of the affected leg and the contralateral normal leg which serves as a control.

Front limbs are tested by having the horse stand quietly with the test leg centred over the force plate, and the contralateral front leg held up. Each leg is tested 4 times, and on each test day both front limbs are evaluated. The horses in this study were referred to the Sterivet Research Centre by local veterinarians. In order to be accepted into the study, horses had to have lameness in one front limb only, and in either the carpus or the fetlock joint only. Twenty-four horses participated in all. Four served as untreated controls, two of which were subsequently treated and re-evaluated on the force plate. Therefore twenty-two horses were evaluated prior to Synacid treatment and for 3 weeks following treatment.

Treatments consisted of a single intra-articular injection of 50 mg of Synacid.

There were 23 Standardbreds and 1 Thoroughbred, 16 geldings, 6 females and 2 males, ranging in age between 2 and 13 years. Diagnosis was based on clinical examination, force plate measurements, radiographs and in 8 cases on desensitization of the affected joint. Twenty-two horses were in active training or racing and 2 horses were in light training only. Fourteen horses were

treated for carpal joint dysfunction and 10 for front fetlock joint disease. The breakdown of joints treated is summarized in Table 6.

Table 6 Force Plate Clinical Efficacy Study: Distribution of Joints Treated

Joint	Left	Right	Total
Carpus	5	9	14
Front Fetlock	7	3	10
TOTAL	12	12	24

Five of the horses with right carpal lameness were treated in both the radiocarpal and intercarpal joint spaces, and two horses with left carpal involvement received radiocarpal and intercarpal joint injections. Therefore in the 14 horses with carpal joint arthritis, 12 intercarpal joints and 9 radiocarpal joints were treated, as illustrated in Table 7.

Table 7 Force Plate Clinical Efficacy Study: Distribution of Carpal Joint Treatments

Side	RC	IC	RC & IC
Left	0	3	2
Right	2	2	5
TOTAL	2	5	7

RC Radiocarpal joint

IC Intercarpal joint

RC & IC Both radio- and intercarpal joints

Observations

Radiographs were taken prior to Synacid treatment. Most horses had evidence of degenerative joint disease of mild to moderate severity. Only one horse had clinical carpalitis with no radiographic lesions.

Synovial fluid samples were taken pre-treatment and at the end of the evaluation period. Samples were submitted for analysis to Chesapeake Biological Laboratories, Huntsville, Maryland under the direction of Dr. W. Tew.

Force Plate assessments were made before treatment and at days 5, 10, 15 and 20 post-treatment, or at 4, 8, 12, 16 and 20 days. Clinical assessments were also made at each evaluation period.

Eight of the horses were injected intra-articularly with a local anesthetic after their pre-treatment force plate assessment but prior to Synacid treatment. Force plate measurements were repeated when the joint was desensitized.

Results

For the purpose of statistical analysis, only those twenty horses not originally serving as controls are used. Sound (control) limb readings on the force plate remained much the same throughout the evaluation period. Unsound limbs had significantly higher FPU values (2.57) than sound control limbs (1.50)

prior to Synacid treatment. A significant reduction ($p < \text{or} = 0.01$) in FPU of the treated limbs was apparent by the first visit following Synacid treatment, when the FPU of treated limbs had decreased from 2.57 to 1.75. The mean FPU of treated limbs continued to decrease progressively following Synacid treatment and by the 5th and 6th visits (days 15 - 17 and days 20 - 21 after Synacid treatment), the FPU of treated limbs was statistically the same as the control limbs. The mean FPU of treated limbs was 1.44 and 1.33 at the 5th and 6th visits, respectively, while the corresponding mean FPU of control limbs was 1.46 and 1.35 at those intervals. The mean FPU values of the sound and unsound limbs of the 20 horses treated is provided in Table 8.

Table 8 Force Plate Clinical Efficacy Study: Mean FPU of 20 Synacid Treated Horses

Day of Visit	Control or Sound Legs	Unsound, Treated Legs
Day 0	1.50	2.57
Days 4-5	1.41	1.75
Days 8-9	1.40	1.51
Days 12-13	1.29	1.36
Days 15-17	1.46	1.44
Days 20-21	1.35	1.33

0 = Pre-injection
 4-21 = Post-injection

The four untreated control horses had similar FPU values as the main group of horses: sound limbs had a mean FPU of 1.2994, compared to 2.4177 in unsound limbs. During the 3 week no treatment evaluation period, the FPU values of the unsound limbs did not decrease, and was 2.5129 at the end of 3 weeks. The two control horses which were subsequently treated with Synacid and evaluated for another 3 week period, did show reduction in the FPU of their unsound limbs following treatment. This data is summarized in Table 9.

Table 9 Force Plate Clinical Efficacy Study: Mean FPU of Control Horses

Evaluation	Visit Days	Sound Legs	Unsound Legs
No Treatment Phase (N = 4)	0	1.2994	2.4177
	5-7 days	1.2612	2.4555
	9-11 days	1.2571	2.4956
	19-21 days	1.2536	2.5129
Treatment Phase (n = 2)	0	1.2943	2.5845
	4 days	1.2665	1.7515
	8 days	1.2645	1.6409
	12 days	1.2142	1.4715
	16 days	1.1641	1.1866
	20 days	1.4780	1.1602

0 = Pre-injection
 4-20 = Post-injection

These results indicate that the improvement in lameness during the three week study period was attributable to Synacid treatment, as lack of training alone did not cause FPU values and lameness to decrease.

The effect of intra-articular anesthesia on lame joints (prior to Synacid treatment) was to reduce the FPU values. FPU values of anesthetized unsound limbs became equivalent to the FPU values of the contralateral controls. This procedure showed that the FPU is a sensitive measurement of the amount of lameness present and that FPU decreases when the limb becomes sounder. Therefore, the Synacid treatment had the same effect in 3 weeks as the intra-articular anesthetic. Table 10 shows the effect of the intra-articular anesthetic on the lame limbs for the 8 horses who underwent this procedure.

Table 10 Force Plate Clinical Efficacy Study: Effect of Intra-Articular Anesthesia of Lame Joint on FPU

Horse	Lame Limb FPU – Pre-Anes. ⁺	Lame Limb FPU – Post-Anes. ⁺	Sound Limb FPU ⁺
1	2.0337	1.6685	1.5886
2	1.8521	1.2773	1.2016
3	2.3454	1.4152	1.4690
4	2.4825	1.1723	1.3024
5	2.0170	1.2823	1.2228
6	2.5311	1.1913	1.2372
7	2.6063	1.3158	1.3017
8	2.5190	1.2953	1.2090
Mean	2.2981	1.3272	1.3165

* each value is the mean FPU of 4 readings.
 Anes = intra-articular anesthetic

The clinical assessments of lameness correlated closely with the FPU values obtained on the force plate. A substantial alleviation of lameness and of other clinical signs of joint inflammation such as heat, effusion and pain on flexion, was evident at the first evaluation following Synacid treatment. No untoward effects of Synacid injection occurred in any of the horses. One horse experienced a transient increase in heat and soreness 2 days after injection, which did not interfere with a successful outcome of treatment.

The response to treatment was considered to be subsatisfactory in only one horse, although substantial improvement was evident compared to pre-treatment, as reflected by decreasing FPU and clinically.

Synovial fluid analysis did not correlate well with degree of lameness, nor with radiographic abnormality. However in the case of the nine joints in this study which had elevated (> 10 mg/ml) protein values, seven returned to normal (< 10 mg/ml) following Synacid treatment.

Conclusion

The conclusion that can be drawn from this study is that a single intra-articular injection of Synacid is effective and safe in the treatment of degenerative joint disease and other arthritic-type conditions in equine carpal and fetlock joints.

3. Positive Controlled Clinical Field Trial

The purpose of this study was to compare the efficacy of the new drug, Synacid, with the efficacy of an approved and closely related drug available on the market.

The study was conducted in two separate geographical centres in the United States. The practices involved were:

1. Drs. David and Norwood, 539 Bonnabel Blvd., Metairie, Louisiana, 70005
2. Drs. Arthur and Pairk, 176; W. Pomona Avenue, Monrovia, California, 91016

Both study locations admitted Thoroughbred race horses only, and treated carpal joints only. Diagnosis of carpal joint dysfunction was based on clinical and radiographic examination and in some cases on intra-articular anesthesia of the joint.

Each study location had at least two participating veterinarians to enable blinding. One veterinarian administered the treatment, and another veterinarian performed the clinical evaluations.

Horses received either 50 mg Synacid or an approved and closely related control drug as a treatment, according to a predetermined computer generated randomization sequence. Both treatments were administered intra-articularly at their respective recommended therapeutic doses.

At the initial visit, horses were carefully evaluated as per the following inclusion criteria:

1. unilateral lameness of carpal joint origin.
2. duration of lameness less than or equal to 3 months.
3. detailed medical histories available.
4. no orthopedic surgery within the previous 4 months.
5. no intra-articular corticosteroid treatment in the preceding 60 days.
6. lameness visually detectable at the jog.
7. actively training or racing.
8. no slab fractures.
9. 2 - 5 year old horses.

Only horses which fit these requirements were admitted into the study.

The study duration was two weeks, with 5 post-treatment follow-up visits at 1, 3, 5, 7 and 14 days. The key follow-up visits with respect to drug efficacy were at 7 and 14 days. The focus of the 1, 3, and 5 day post-treatment visits was to evaluate drug safety.

A repeat treatment at the one week visit was optional depending on response.

Observations

Synovial fluid analysis was performed by Dr. W. Tew of Chesapeake Biological Laboratories, Maryland, on samples taken prior to treatment and at 1 week post-treatment. If a repeat treatment was administered, then a third synovial fluid analysis was carried out at the two week post-treatment visit.

Observations were made on joint heat, joint effusion, joint circumference, pain response on passive joint flexion, pain response on joint palpation and lameness grade. Data recording was made objective and uniform among the study centres by providing numerical scoring systems and by establishing anatomical landmarks for joint circumference measurements. Heat and pain responses to flexion and palpation were standardized by comparison with the contralateral sound limbs.

The numerical codes used were as follows:

Heat

- 0 =absent;
- 1 =slight;
- 2 =mild;
- 3 =moderate;
- 4 =severe.

Heat evaluations were based on the difference between the sound carpus and the lame carpus, and were made prior to exercise.

Effusion

- 0 =absent;
- 1 =detectable on careful palpation of the joint;
- 2 =obvious joint capsule distension;
- 3 =severe joint capsule distension grossly visible at a distance.

Lameness

Grade

- 0 = sound, no detectable lameness;
- 1 = slight lameness, detectable by an expert only;
- 2 = lameness observed at a jog and consistently apparent under certain circumstances such as weight-bearing, circling;
- 3 = lameness observed under all circumstances, and at the walk;
- 4 = three-legged lameness or minimal weight-bearing.

Subjective assessments were also made regarding improvement in performance and overall response to treatment.

Data from each study centre was analyzed separately and then combined for a composite analysis. This discussion is confined to the composite analysis.

Results

Thirty-seven horses were treated in the study, with 19 having received Synacid and 18 having received the control drug, as shown below in Table 11A.

Table 11B lists the demographic and medical history variables of the horses.

Table 11A Positive Controlled Clinical Field Trial: Disposition of Cases

	CC-2	CC-3	Total
Synacid	10	9	19
Control Drug	10	8	18
Total	20	17	37

Table 11B Positive Controlled Clinical Field Trial: Demographic and Medical History Variables Variables Synacid Control Drug n = 19 n = 18

Variables	Synacid n=19	Control Drug n=18
Sex: female	9	10
Sex: male	3	2
Sex: gelding	7	6
Mean age: (years)	3.2	3.0
Race winners	10	10
Nonwinners	9	8
Duration of lameness: <2 weeks	9	8
Duration of lameness: 2 weeks-3 months	10	10
Onset of lameness: acute	12	10
Onset of lameness: insidious	7	8
Joint treated: intercarpal	6	10
Joint treated: radiocarpal	8	2
Joint treated: both	5	6

The data in Table 11B shows that the Synacid and control drug treated horses were similar with respect to the variables on medical history, prior to treatment.

Lameness Grade and Joint Circumference

Two dependent variables, lameness grade and joint circumference, were selected/or statistical analysis.

Mean lameness grade values at each observation and changes from baseline at the two post-treatment observations are provided in Table 12. An analysis of

variance was used to determine if the changes from baseline values were statistically significant.

The treatment groups were not statistically different with respect to mean lameness grade scores at baseline, as well as at weeks one and two post-treatment. Averaging weeks one and lameness grades were significantly lower ($p < \text{or} = 0.01$) post-treatment in both the Synacid and control groups.

Therefore both drugs had a comparable effect in reducing lameness.

Table 12 Positive Controlled Clinical Field Trial: Analysis of Lameness Grade

Observation	Synacid	Control Drug
Baseline (Week 0)	n=19	n=18
Baseline (Week 0) – Mean Score	2.89	2.92
Week 1	n=19	n=18
Week 1 – Mean Score	1.76	1.97
Week 1 – Mean Change	-1.13	-0.94
Week 2	n=19	n=16
Week 2 – Mean Score	1.63	1.34
Week 2 – Mean Change	-1.26	-1.44

Joints with a clinical soft tissue swelling were measured at each observation period using a flexible tailor's tape. Joint circumference measurements were also made on the contralateral normal joints. Radiocarpal and intercarpal joints are considered separately because of different anatomical sizes. Differences between treated and contralateral joints were calculated. This data is displayed in Table 13.

At baseline joints with soft tissue swelling measured approximately 1 cm more than unaffected contralateral joints. At one week after treatment this difference (TJ-CJ) was reduced to 0.5 cm in the Synacid group, but remained unchanged in the control group. The improvement in joint size in the Synacid group is also reflected in the actual measurements of treated radiocarpal and intercarpal joints at week one. Further reduction did not occur after week one in the Synacid treated horses as can be seen from the week two data.

Control drug treated joints which had not responded at week one did undergo a modest improvement by week two for radiocarpal joints only in that the difference between treated and contralateral joints (TJ-CJ) was 0.72 compared to a TJ-CJ of 0.97 at baseline.

Table 13 Positive Controlled Clinical Field Trial: Joint Circumference Measurements in Centimeters at Baseline, Week One, and Week Two

		Synacid	Control Drug
Baseline	Radiocarpal Joint	n=8	n=7
	Radiocarpal Joint – Treated	33.41	32.60
	Radiocarpal Joint – Contralateral	32.13	31.63
	Radiocarpal Joint – TJ-CJ	1.28	0.97
	Intercarpal Joint	n=8	n=7
	Intercarpal Joint – Treated	30.80	30.90
	Intercarpal Joint – Contralateral	29.64	30.12
	Intercarpal Joint – TJ-CJ	1.16	0.78
Week One	Radiocarpal Joint	n=8	n=7
	Radiocarpal Joint – Treated	32.74	32.44
	Radiocarpal Joint – Contralateral	32.23	30.12
	Radiocarpal Joint – TJ-CJ	1.16	0.78
	Intercarpal Joint	n=8	n=11
	Intercarpal Joint – Treated	30.25	30.58
	Intercarpal Joint – Contralateral	29.73	29.77
	Intercarpal Joint – TJ-CJ	0.52	0.81
Week Two	Radiocarpal Joint	n=8	n=5
	Radiocarpal Joint – Treated	32.78	32.24
	Radiocarpal Joint – Contralateral	32.19	31.52
	Radiocarpal Joint – TJ-CJ	0.59	0.72
	Intercarpal Joint	n=8	n=9
	Intercarpal Joint – Treated	30.29	30.74
	Intercarpal Joint – Contralateral	29.78	29.98
	Intercarpal Joint – TJ-CJ	0.51	0.76

TJ-CJ = Treated joint circumference minus contralateral joint circumference.

Joint Heat and Effusion

The mean values for the clinical parameters of joint heat and joint effusion are provided in Table 14, along with the changes from baseline. Joint heat and effusion resolved more rapidly in the Synacid treated group than in the control group. Mean changes from baseline at week one were -0.79 for joint heat and -0.63 for joint effusion in the Synacid treated group compared to corresponding values of -0.39 and -0.42 in the control group. Heat and effusion remained static in the Synacid group between weeks one and two whereas progressive improvement occurred in the control group, such that at two weeks the effect of both drugs was virtually identical.

Table 14 Positive Controlled Clinical Field Trial: Joint Heat and Effusion

Observation	Parameter	Synacid Mean Score	Synacid Mean Change from Baseline	Control Drug Mean Score	Control Drug Mean Change from Baseline
Baseline	Heat	2.0		1.9	
Baseline	Effusion	1.7		1.8	
Week One	Heat	1.2	-0.79	1.5	-0.39
Week One	Effusion	1.1	-0.63	1.4	-0.42
Week Two	Heat	1.0	-1.00	1.1	-0.63
Week Two	Effusion	1.1	-0.63	1.1	-0.63

Synovial Fluid Analysis

Joints with elevated synovial fluid protein (> 10 mg/ml) and reduced synovial fluid viscosity (< 22) were evaluated for changes over the study period. Reductions in synovial fluid protein and increases in viscosity are considered to be the desirable changes. However synovial fluid characteristics are variable and prone to many physiological fluctuations.

Synovial fluid protein had decreased in both treatment groups at week 2, but only in the Synacid treated horses at week one. These changes are difficult to interpret clinically because the sample size is small, as is the magnitude of the changes observed.

Synovial Fluid viscosity did not increase following treatment with either drug. This result is not surprising in light of the erratic data and the large standard deviations. The small decreases in joint viscosity experienced in both treatment groups are not clinically important and the conclusion is that neither drug affected synovial fluid viscosity.

Table 15 summarizes the data on synovial fluid protein and viscosity.

Table 15 Positive Controlled Clinical Field Trial: Synovial Fluid Protein and Viscosity

Parameter	Synacid Mean Score	Synacid n	Control Drug Mean Score	Control Drug n
Protein Pre-treatment	13.59	7	12.72	9
Protein Week 1	9.93	5	13.06	5
Protein Week 2	11.50	1	10.20	3
Viscosity Pre-treatment	8.02	24	7.55	24
Viscosity Week 1	5.30	23	6.26	24
Viscosity Week 2	5.70	3	5.03	7

Subjective Evaluation

Overall response to treatment was subjectively evaluated by the veterinarians as either 'good', 'fair' or 'poor'. Treatment failures were counted as those horses who were rated as having a 'poor' response at the end of 2 weeks. Nineteen Synacid and 16 control drug treated horses were categorized at the end of the study. In the 'good' category there were 10 Synacid and 12 control drug horses. The 'fair' category had 8 Synacid and 4 control drug horses. The single treatment failure or 'poor' response was a Synacid treated horse.

There were 10 horses in total, 3 from the Synacid group and 7 from the control drug group, that were reinjected at one week following the initial treatment. In most instances, a repeat injection was found to enhance the therapeutic benefit of the first drug treatment.

Safety

Data from the 1, 3, and 5 day post-treatment follow-up visits was relevant to the safety of the two drugs used in this study. If clinical signs were exacerbated following treatment, the veterinarians indicated that a 'joint flare' had occurred. There was a low rate of such occurrences in both treatment groups, 3 and 2 incidences for Synacid and the control drug, respectively. In all 5 cases, the joint flares were classed as transient and minor and resolved spontaneously within 24 to 96 hours. These effects can be anticipated following any intra-articular procedure.

Conclusions

This study demonstrated that the new drug Synacid is equivalent in efficacy and safety to the control drug. Treatment with each drug resulted in significant therapeutic benefit. Improvement occurred in lameness and in the other clinical signs of inflammation. No apparent differences were found between Synacid and the control drug with respect to any of the efficacy or safety

parameters studied, and no untoward effects resulted from treatment with either drug.

B. Corroborative Field Studies

The purpose of this field trial was to evaluate the effectiveness of Synacid in a variety of joints with osteoarthritis and under conditions of use encountered in the field.

Eleven veterinarians participated in this trial representing a good cross section of geographical locations and equine breed and function.

The names and addresses of the investigators are:

Dr. A. Kent Allen
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Box 749
Gilbert, Arizona 85234

Dr. Richard Balmer
96 Middletown Road
Holmdel, New Jersey 07733

Dr. Richard A. Frank
Windview Acres
R.D. 1
Stillwater, New York 12170

Dr. Daniel Marks
Delaware Equine Centre
R.D. 2
Cochranville, Pa. 19330

Dr. Larry Metheney
19020 N 22nd Street
Phoenix, Arizona 85024

Dr. Gary Norwood
Back-Stretch Surgery and Medicine Inc.
539 Bonnabel Blvd.
Metairie, La. 70005

Dr. William O. Reed
111 Plainfield Avenue
Elmont, New York 11003

Dr. R.J. Shive
Penn Hills Equine Hospital
R.R. 4
Shubenacadie, Nova Scotia

Dr. Janice Sosnowski
Brenford Animal Hospital
2206 N duPont Highway
Dover, Delaware 19901

Dr. John R. Steele
Box 483
Youngs Road
Vernon, New York 13476

Dr. H. Valdez
Equine Sports Surgery Centre
King Street
Uxbridge, Mass. 01569

The study was conducted in the form of an open field trial with each horse acting as his own historical control. Placebo treatments were considered unethical and an approved related drug was not available when the study commenced.

Horses received a full pre-treatment clinical and radiographic evaluation to obtain the diagnosis of joint disease. Horses with intra-articular fractures (except chip fractures) and septic joints were not admitted into the study.

A total of 397 separate joints (carpus = 156, fetlock = 117, hock = 113, stifle = 8, coffin = 3) were treated in 236 horses and filed on 375 case report forms. Twenty-three horses were introduced into the study as new cases sometime over the two year study duration. Thus there were 259 cases studied.

The majority of cases treated were racing Standardbreds (207) and racing Thoroughbreds (152). Among the remaining 33 horses, there were show jumpers, event horses and 20 working Quarterhorses. The average age of horses in this study was 4.9 years old. There were 132 females, 90 males, 170 geldings and undetermined. In 205 cases, the left limb was affected and in 192 cases the right limb was affected.

The difference between the number of horses treated (236) and the number of joints treated (397) is due to the incidence of bilateral or multiple joint problems in one horse. Unilateral joint dysfunction was present in 136 animals. In the remaining 100 animals some form of multiple dysfunction was present and more than one joint was injected.

Some veterinarians elected to report horses with 2 joints treated on a single case report form. This accounts for the difference between joints treated (397) and case reports filed (375).

Case Reports Filed	Horses Treated	Separate Joints Treated
136	136	136
189	98	211
50	25	20
375	259	397

Treatments consisted of intra-articular injection of 50 mg (5 ml) of Synacid 10 mg/ml, which is the labelled dose. Some exceptions occurred in hock joints, in which the total dose (50 mg) was occasionally divided between two small joint spaces, such as the distal intertarsal and tarsometatarsal spaces.

A second injection was optional at two weeks, if the veterinarian felt that response was not optimal.

Data was gathered in two trial formats. Series A involved follow-ups post-treatment, at 1, 2 and 4 weeks and at 3 months. Series B data was collected weekly for 6 consecutive weeks post-treatment. The two week and four week data from each series were combined for analysis of efficacy.

Observations

The following parameters were ranked by the veterinarians during the horses initial and follow-up visits:

1. Joint Heat: 0 = Absent; 1 = slight; 2 = moderate; 3 = severe.
2. Joint Swelling: 0 = Absent; 1 = slight; 2 = moderate; 3 = severe.
3. Excessive Fluid: 0 = Absent; 1 = slight; 2 = moderate; 3 = severe.
4. Pain on Flexion: present = yes; absent = no.
5. Pain on Palpation: present = yes; absent = no.
6. Functional Disorder (Lameness):
 1. Horse is racing/performing sound.
 2. Symptoms present only during extreme stress or work.
 3. Symptoms present only when in motion and when joint used, but not while standing.
 4. Symptoms present when standing and refusing to place full weight on joint under any condition.

Results

Results were analyzed for the combined number of joints (397) as well as separately for carpal joints (156) and fetlock joints (117) since the latter two joints were studied extensively in pivotal efficacy studies.

In the case of swelling, heat, excessive fluid and functional disorder, mean scores were lower at 2 and 4 weeks than prior to treatment, as shown in Table 16.

As well, fewer horses had pain on joint flexion and pain on joint palpation 2 and 4 weeks following Synacid injection compared to pre-treatment. These results are also summarized in Table 16, as the actual number of horses, and percent of horses in parentheses, that were abnormal (had a 'yes' response) prior to treatment, and the number of horses and percent of horses in parentheses that improved at weeks 2 and 4.

A final performance evaluation was completed at the last followup visit, corresponding to 6 weeks in Series A and 90 to 120 days in Series B. Categories for final performance evaluation were:

- Good: Horse resumed same level of activity as prior to treatment and remained racing sound for at least 3 months.

- Fair: Resumed same or slightly lower level of activity/performance as prior to treatment but symptoms returned in less than 3 months.
- Poor: Horse continued lame and/or unable to perform within 2 weeks of second treatment with Synacid.

Since final performance was a subjective evaluation, a statistical analysis of this data was not considered necessary. Results were tabulated as number of horses (and percent of horses) in each category (good, fair, poor). Total improvement was taken as the sum of 'good' and 'fair' responses.

Of 187 joints evaluated in Series A, 117 (63%) were rated as 'good' and 60 (32%) were rated as 'fair', yielding an improvement of 177 or 95%. Ten cases (5%) were evaluated as 'poor'.

Series B final performance evaluation data on 149 joints was similar, with 98 cases (66%) in the 'good' category, 50 (33%) in the 'fair' category and 1 horse (1%) in the 'poor' category. Total improvement in Series B was 148 cases, or 99%.

Therefore a single intra-articular injection of Synacid was found to have a beneficial effect on performance as long as 90 days after treatment. These results are summarized in Table 17.

Table 16 Corroborative Field Study: Table of Means of Response Parameters

Exam	Joint* Swollen	Joint* Hot	Excessive* Fluid	Functional* Disorder	Pain On** Flexion	Pain On** Palpation
All Joints Baseline	0.8	0.5	1.1	2.6	287 (71)*	210 (53)
All Joints 2 Weeks	0.5	0.1	0.4	1.8	164 (61)	114 (56)
All Joints 4 Weeks	0.4	0.1	0.3	1.6	206 (79)	141 (73)
Carpus Baseline	0.9	0.6	1.0	2.6	87 (56)	102 (65)
Carpus 2 Weeks	0.6	0.2	0.5	1.8	62 (75)	53 (54)
Carpus 4 Weeks	0.5	0.1	0.4	1.6	71 (88)	69 (77)
Fetlock Joint Baseline	1.1	0.6	1.4	2.7	111 (95)	40 (34)
Fetlock Joint 2 Weeks	0.5	0.2	0.6	1.9	50 (47)	24 (60)
Fetlock Joint 4 Weeks	0.4	0.1	0.6	1.6	69 (68)	26 (68)

* figures provided are mean scores

** figures provided are number (percent) of horses abnormal at baseline, and number (percent) improved at weeks 2 and 4.

Table 17 Corroborative Field Trial: Summary of Final Performance Evaluation by Study Duration n = 187 n = 149 Category Series A Series B Total

Category	n=187 Series A	n=149 Series B	Total
Good	117 (63)*	98 (66)	215 (64)
Fair	60 (32)	50 (33)	110 (33)
Poor	10 (5)	1 (1)	11 (3)
Total Improvement	117 (95)	148 (99)	325 (97)

* values are number (percent) of horses.

The final performance evaluation was comparable in carpal and fetlock joints. The total improvement (good and fair responses) was 98% and 94% in carpi and fetlock joints respectively. Refer to Table 18.

Table 18 Corroborative Field Trial: Summary of Final Performance Evaluation by Joint

Category	n=129 Carpus	n=101 Fetlock Joint
Good	80 (62)*	67 (66)
Fair	47 (36)	28 (28)
Poor	2 (2)	6 (6)
Total Improvement	127 (98)	95 (94)

* values are number (percent) of horses.

Eleven joints were rated as 'poor' or treatment failures on the final performance evaluation. This represents 3% of the total joints treated. Two of the treatment failures were carpal joints, representing approximately 2% of the 129 carpi, and six (approximately 6%) were fetlock joints. The 11 treatment failures occurred in 9 horses and were reported by four of the investigators. Most treatment failures underwent improvement in at least one abnormal clinical sign. However in these cases functional disorder did not improve substantially with the resolution of other clinical signs.

Results: Safety

No untoward reactions occurred as a result of treatment, except such as can be expected following routine joint invasion. Six (2.3%) of the 236 horses treated experienced minor drug related side effects (such as transient increases in heat or effusion) and 4 horses (1.7%) experienced reactions in which increased lameness was also a component. Lameness in these 4 horses resolved rapidly with adjunctive therapy. All reactions were reversible and none were associated with systemic signs or joint sepsis.

Conclusion

The multicentre open field trials serve to support the efficacy and safety of Synacid as previously established in pivotal well-controlled studies on a smaller number of equine patients. The field trials also support the proposed labeling by demonstrating significant and comparable efficacy in carpal and fetlock joints following a single intra-articular injection of 50 mg of Synacid.

III. TARGET ANIMAL SAFETY

Safety studies were conducted in laboratory animal species and in the target equine species. Only equine safety studies are included in this section as they are relevant to the intended use of Synacid. The three equine safety studies included:

1. an acute systemic toxicity study at 4X to 60X the recommended dose
2. an acute local (intra-articular) toxicity study at 1.5X and 3X the recommended dose and
3. a subacute systemic toxicity study in which 2X the recommended dose was administered for six injections.

A. Pivotal Studies

1. A Systemic Toxicological Evaluation of Synacid

The purpose of this subacute toxicity study was to determine the systemic toxicological profile of Synacid when administered by the recommended route (intra-articular) at two times the recommended dose of 50 mg and for a total of six treatments.

The study was conducted by Dr. A. Aviad at the Sterivet Research Centre, Dundas, Ontario between April and July, 1985.

Seven mature non-athletic Standardbred horses obtained locally served as the experimental animals. During the acclimation period prior to study commencement, horses received a complete physical examination and were dewormed with a suitable broad spectrum anthelmintic. There were 3 mares, 3 geldings and 1 stallion, all of which were in good general health and free of lameness. Horses were housed in individual loose box stalls and fed a weight maintenance ration consisting of hay, oats and water for the duration of the study. Except on treatment days, horses were exercised daily by walking on a mechanical hot walker at medium speed for 1 hour.

All treatments consisted of 100 mg of Synacid (sodium hyaluronate injection 10 mg/ml) injected intra-articularly. The 100 mg dose (2X the recommended dose of 50 mg) was equally divided between the left radio- and intercarpal joint spaces in order to accommodate the total volume. Treatments were repeated every two weeks for a total of 6 injections. Right sided radio- and intercarpal joints served as untreated controls.

Observations

The parameters studied were related either to systemic effects or to local effects of treatment.

Systemic toxicity evaluations consisted of:

1. BSP Clearance test: performed twice prior to the first treatment, after 3 treatments and after 6 treatments.
2. Hemograms and clinical chemistry profiles: performed prior to each injection and following the last injection. Blood samples were also submitted from an untreated control. The control horse was a non-

athletic Standardbred which came from the same background as the test horses.

3. Physical examination of the horses for clinical signs of toxicity: performed for 3 consecutive days following each treatment. Cardiovascular, respiratory, digestive and central nervous system function was carefully examined in this category. General well being was assessed by attitude, appetite, periods of recumbency, and appearance of hair coat.
4. Body weight: taken twice a month.

Local effects of intra-articular treatment were monitored by:

1. Synovial fluid analysis: performed prior to each treatment and 2 weeks following the last treatment.
2. Physical examination of gait and of heat, swelling and effusion: performed prior to each treatment and at 4, 8, 24, 48 and 72 hours following each treatment.
3. Joint circumference measurements: performed at the same intervals as the clinical joint evaluation in # 2 above.
4. Radiographic examination; performed prior to the first treatment and at the study's conclusion.

All observations on local effects, including synovial fluid analysis and radiographs, were made on treated (left-sided) joints and on control (right-sided) joints.

All biological samples were analyzed within 24 hours at accredited laboratories.

Data on quantitative parameters was analyzed using an analysis of variance.

Results: Systemic Effects

Body Weight

No clinically or statistically significant changes occurred in body weight. Mean body weight was 939 lbs prior to treatment, and 943 lbs one week after the last injection.

BSP Clearance

All the BSP Clearance tests were within normal range. There was little variability in results between horses, and no statistically significant changes were noted at the post-treatment sampling intervals.

Physical Examination

All vital signs (temperature, pulse, respiration) and other clinical findings were normal at each evaluation period with the exception of an isolated incidence of constipation during which the horse affected had decreased appetite and fecal output and increased recumbency.

There were no significant differences in pulse or respiratory rates at any post-treatment evaluation period, compared to pretreatment values.

Statistically significant changes were found in the means of body temperature. However no clinical meaning is attached to this finding since all body temperatures were normal (between 99° and 100°F at every observation).

Hematology and Clinical Chemistry

There were no indications of systemic toxicity after six Synacid treatments of 100 mg each.

Most of the values for blood parameters were within the normal equine range. Some values consistently fell outside the laboratory reference range. These values were considered to be normal for the type of horse used in this study (non-athletic) since they occurred prior to treatment as frequently as following treatment and in both the control and the treated horses.

Numerous changes from pre-treatment values were noted during the course of the study in the treated horses as well as in the control horse. Statistical significance based on a paired t-test was often found with respect to these changes. However, these changes resulted from physiological fluctuations within normal limits and have no clinical importance.

Results: Local Effects

Treatments did not result in any adverse local reactions or signs of toxicity. There was no evidence of soreness at the injection site no infections, no lameness and no acute inflammatory responses.

Radiographs

Post-treatment radiographs taken 1 week after the sixth and final intra-articular Synacid injections did not reveal any bony or tissue changes within the joints.

Gait

There were no instances of unsoundness in any of the horses at any evaluation period.

Gross Appearance

There were no significant abnormalities of overall joint appearance. Twenty-four hours after the 6th injection, one horse had a 'puffy' left carpus. Another horse was judged to have a swollen left carpus 48 and 72 hours after the second injection.

Joint Circumference

Prior to every injection, no statistically significant differences were found between treated and control joints. This indicates that there are no long term effects on joint size as a result of multiple Synacid injections.

Statistical analysis of joint circumference measurements at hourly intervals post-treatment demonstrated no significant differences between treated and control joints prior to the last injection.

At 24 and 48 hours following the last (6th) injection, treated joints had a small magnitude but statistically significant increase in joint Circumference compared to control joints. At 72 hours the treated joints were the same as the control joints. Therefore the small magnitude increases in joint size were of a transient nature.

Heat, Swelling, Effusion

Minor and transient increases in effusion, heat and soft tissue swelling occurred sporadically at 24 to 72 hours following treatment.

Differences between treated joints and control joints with respect to these parameters were inconsistent prior to the 4th injection. After the fourth injection the repeated insult to the joints, caused by frequent arthrocentesis and joint capsule distension, produced a minor but noticeable treatment effect. These results are anticipated following routine joint injections due to the trauma of the procedure.

Synovial Fluid Analysis

No significant differences with respect to changes from baseline values were found between treated and control joints in the analysis of mucin clot and protein content. White blood cell counts were normal and showed no changes throughout the study period.

Viscosity and hyaluronate content were reduced at the end of the study compared to pre-treatment values in both treated and control joints. These changes are ascribed to the cumulative trauma of frequent arthrocentesis. Treated radiocarpal joints were not different than control radiocarpal joints with respect to hyaluronate content at any time during the study. Treated intercarpal joints were found to have significantly lower hyaluronate content than control intercarpals after the last injection only. Both treated radiocarpal and intercarpal joints had significantly lower viscosity than control joints following the last injection.

Conclusions

This subacute toxicity study demonstrates the safety of 6 serial Synacid injections administered at 2X the recommended dose. No adverse reactions and no signs of systemic or local toxicity occurred. Treatment did not produce any drug related side effects with respect to parameters monitored in the category of systemic safety. Local side effects were observed after the 4th injection, but were minor, reversible changes of no clinical consequence. These changes are more appropriately described as trauma-related than as drug-related side effects.

B. Corroborative Safety Studies

1. Systemic Safety of High Doses (600 - 3000 mg/Horse) of IntraArticularly Administered Synacid in Horses

An acute toxicity study was conducted by Clark Billingham, D.V.M., at the Sterivet Research Centre in Dundas, Ontario.

Nine mature Standardbred horses were randomly assigned to one of three treatment groups, with three horses per group. Group 1 received 200 mg of Synacid by intra-articular injection weekly for 3 weeks. Group 2 and group 3 horses were injected with 600 mg and 1000 mg, respectively, on the same occasions. Therefore each treatment constituted 4X, 12X and 20X the recommended therapeutic dose of .50 mg of Synacid in groups 1, 2 and 3 respectively. Combining the three injections, the total dose administered to groups 1, 2 and 3 was 600, 1800 and 3000 mg of Synacid, respectively, representing 12X, 36X and 60X the recommended dose.

Each treatment consisted of Synacid (hyaluronate sodium 10 mg/ml) divided between any combination of carpal, fetlock and stifle joints to accommodate the total designated dosage.

Observations

Temperature, pulse, joint circumference measurements, and examination for lameness, joint heat and swelling were made prior to and at 4, 8, 24 and 48 hours following each injection. These observations were repeated one week following the final injection.

BSP clearance, prothrombin time, hematology and clinical chemistry tests were performed prior to the first treatment and one week following the third (last) injection. All biological samples were analyzed at accredited laboratories.

Horses in the highest dose group (group 3) were euthanized at the end of the study and necropsied for gross and histopathological examination of vital organs, by Dr. B. Wilcock, D.V.M., PhD, Diplomate, Associate Professor of Pathology, Ontario Veterinary College University of Guelph.

Results

Hematology and Clinical Chemistry

There were no clinically significant abnormal values or changes at the final (Day 21) evaluation compared to pre-injection values.

BSP Clearance

Except for one horse, all post-treatment clearance values were either the same or lower than pre-treatment values. The one exception was not a large change and was not abnormally elevated.

Joint Circumference

No significant changes in either carpal or fetlock joints were found during the observation period. (Stifle joints were not measured.)

Joint Heat and Swelling

No lameness and no clinically significant joint reactions were observed in any joint. A few joints were recorded as warm and/or hours after injection. This was attributed to joint capsule distension by the large volumes injected.

Body Temperature and Heart Rate

No abnormalities in these two vital signs were recorded at any observation period.

Pathology

Gross pathology was absent in all three horses. Histopathological examination revealed no lesions that were related to Synacid treatment.

Conclusions

This acute toxicity study demonstrates the safety of Synacid (hyaluronate sodium injection 10 mg/ml) at doses as high as 60X the recommended dose and at 3X the recommended treatment frequency. High doses of Synacid administered intra-articularly did not produce systemic drug-related side effects nor any untoward local effects.

2. Safety of Intra-Articularly Administered Synacid in Horses

The object of this acute toxicity study was to evaluate the local safety of Synacid using the labelled route of administration (intraarticular) at 1.5X and 3X the recommended dose.

The study was conducted by Clark Billingham, D.V.M. at the Sterivet Research Centre in Dundas, Ontario.

Four mature Standardbred horses whose joints appeared to be normal as assessed by locomotion, palpation and radiographic examination served as the experimental animals.

The study duration was 28 days excluding a two week acclimation period prior to study commencement. Two identical treatments were administered during the study, on Day 0 and again on Day 14. All treatments consisted of intra-articular Synacid (sodium hyaluronate 10 mg/ml) injections at the dose of 75 mg (7.5 ml) into each of the left radiocarpal and left intercarpal joints, and 150 mg (15 ml) into the left femoropatellar (stifle) joint.

Thus on each treatment day the total dose administered was 300 mg Synacid per horse, representing 1.5X the recommended dose in carpal joints and 3X

the recommended dose in stifle joints. Right sided contralateral joints served as controls.

Synovial fluid was withdrawn weekly from treated and control carpal joints. In the control joints half of the fluid obtained on Days 0 and 14 was reinjected to simulate the technique of intra-articular injection. This procedure was not consistently performed on stifle joints due to the difficulty in aspirating synovial fluid from normal stifle joints.

Observations

Blood analysis for hematology and clinical chemistry profiles was performed on Days 0, 7, 14, 18, 21 and 28.

Radiographs were taken prior to the first injection and after the last injection.

Joint circumference was measured prior to treatment and for seven consecutive days following treatment. Final circumference measurements were made 2 weeks after each treatment, Days 14 and 28.

Clinical evaluation of gait and of joint heat and swelling were performed at the same intervals as noted above for joint circumference measurements.

Synovial fluid analysis was performed on treated and control joints on Days 0, 7, 14, 21 and 28. Samples were analyzed for red and white blood cell counts, cytology, protein content and mucinous precipitate quality.

At the end of the study the horses were euthanized for gross and histopathological examination of all treated and control joints.

Results

Radiographs

No changes were observed in the post-treatment radiographs.

Hematology and Clinical Chemistry

Differences were found between pre-treatment and post-treatment samples with respect to the values obtained for all the tests performed.

Synovial Fluid Examination

No changes which could be attributed to Synacid treatment were detected, however modest and inconsistent increases of leukocytes and red cells were noted in synovial fluid from both treated and untreated joints. These changes are attributed to physical trauma due to injection procedures.

IV. 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.

V. AGENCY CONCLUSIONS

The data submitted in support of this New Animal Drug Application comply with the requirements of Section 512 of the Act and 514.111 of the implementing regulations. It demonstrates that Synacid (hyaluronate sodium), when used according to the labeled conditions of use, is safe and effective.

The safe and effective use of Synacid (hyaluronate sodium) injected intra-articularly in horses requires a veterinarian's knowledge of surgical technique and knowledge of the anatomy of the specific joint. Accordingly, a veterinarian is necessary for proper administration and Synacid is classified as a prescription drug.

VI. ATTACHMENTS

Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.