

(continued)

Legend[®]

(hyaluronate sodium)

Injectable Solution

SIDE EFFECTS OR ADVERSE REACTIONS:

No local or systemic side effects were observed in the clinical field trials with either intravenous or intra-articular injections.

PRECAUTIONS:

Radiographic evaluation should be carried out in cases of acute lameness to ensure that the joint is free from serious fractures. As with any intra-articular treatment, special precautions must be followed as to injection technique and sterility for prevention of possible swelling or infection. Intra-articular injections should not be made through skin that has been recently fired or blistered, or that has excessive scurf and counterirritant on it.

WARNING:

Not for use in horses intended for food.

Safety in breeding animals has not been determined with Legend Injectable Solution.

INDICATIONS:

Legend[®] (hyaluronate sodium) 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.

DOSAGE AND ADMINISTRATION:

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.

HOW SUPPLIED:

Code: 0175 Carton containing six 2mL (20mg) vials
79001750, R. 9 December, 2000

Code: 0176 Carton containing six 4mL (40mg) vials
79001760, R. 5 December, 2000

REFERENCE:

¹ Swanstrom, O.G. 1978. Hyaluronate (hyaluronic acid) and its use. Proc. American Assoc. Equine Pract., 24th annual convention, pp. 345-348.

U.S. Patent Nos. 4,782,046 and 4,808,576

Made in U.S.A.

EQUINE JOINT DISEASE



Stop acute damage before
it becomes chronic

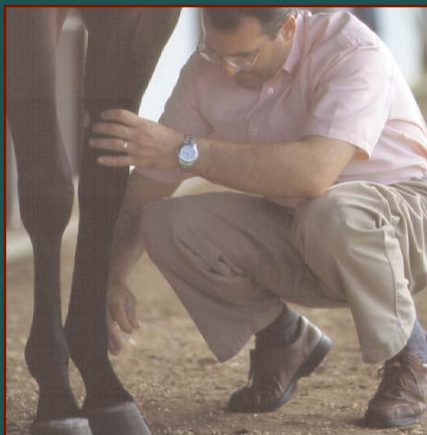


Bayer HealthCare LLC, Animal Health Division
Shawnee Mission, Kansas 66201

LEGEND[®]
(hyaluronate sodium) INJECTABLE SOLUTION

The Only Approved I.V. Joint Therapy

Early recognition is the best way to protect your horse.



*“Trauma to a joint can happen in an instant,
when you least expect it. Or it can happen
slowly when you don’t even suspect it.”*

– LINDY BURCH

NCHA Riders Hall of Fame

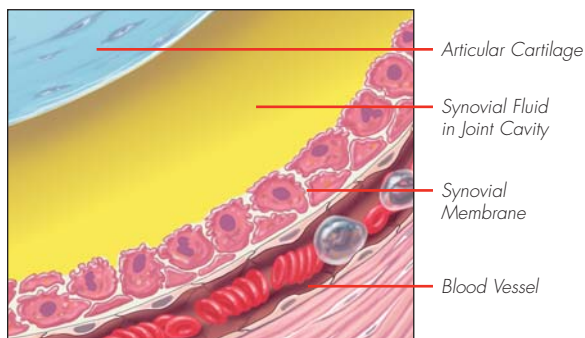
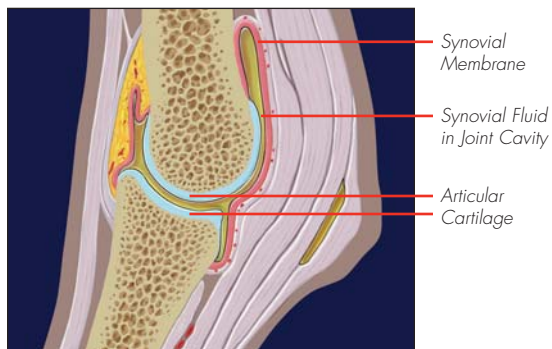
2000 NCHA Open World Championship

First woman president of National Cutting Horse Association

Traumatic joint disease is the leading cause of lameness in horses, and it can happen to any horse at any time. It may be caused by one incident, although it is most likely to appear after repeated episodes of stress and trauma to the joint, particularly in athletic horses.

The effects of traumatic and degenerative joint disease can be devastating, often resulting in poor performance, downtime and economic loss. That’s why early recognition, diagnosis and appropriate treatment are critical to minimize damage to the affected joint.

The healthy joint structure.



The joint is composed of articular cartilage and associated soft tissue structures. The joint cavity is filled with synovial fluid, which lubricates joint surfaces, removes waste materials, and provides nutrition to the cartilage.

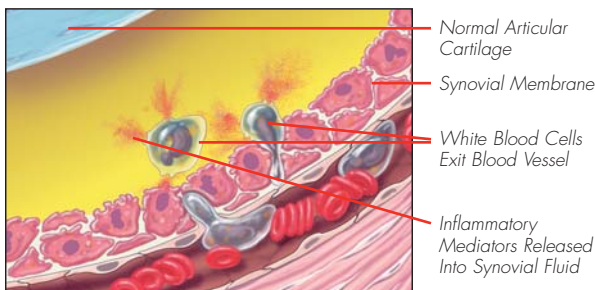
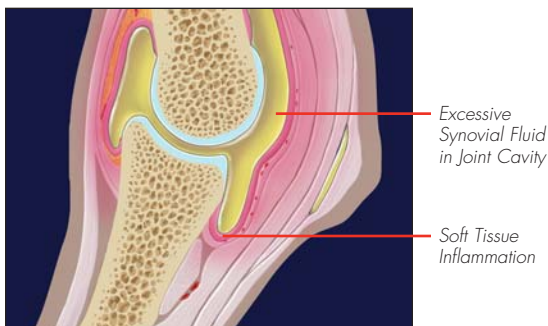
The most common cause of joint inflammation.

Repeated trauma or stress to the joint during everyday use, athletic training or performance is often the initiating cause of joint inflammation.

Early signs of inflammation include:

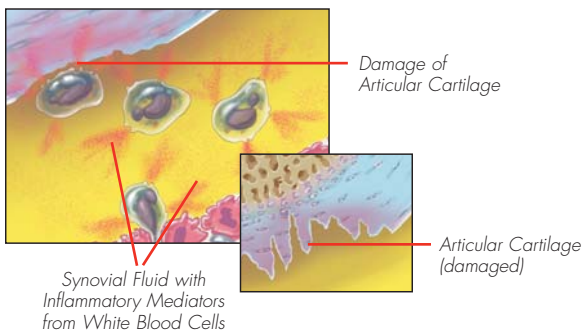
- Heat
- Pain
- Swelling of the joint
- Excessive synovial fluid
- Varying degrees of lameness

Inflamed joint.



Joint disease is a progressive process.

Articular cartilage damage.



Articular cartilage damage can develop into Degenerative Joint Disease (DJD) or osteoarthritis. DJD cannot be corrected, only managed. The objective of early joint therapy is to limit inflammation and block the release of inflammatory mediators. The goal is to normalize the inflamed joint as quickly as possible—before permanent damage occurs.

“The last thing you want to do is ignore early signs of trouble. I’ve seen great potential destroyed by joint disease. I’ve also seen the tremendous advantages of early treatment and careful management.”

– GEORGE MORRIS

USET Show Jumping Team Chef D’Equipe

Common treatment options for Equine Joint Disease.

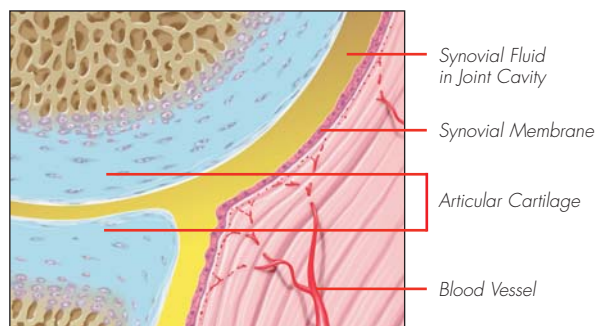
- Rest
- Physical therapy
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Corticosteroid therapy
- Polysulfated glycosaminoglycan (PSGAG)
- Hyaluronic acid (HA)

The Benefits of HA Therapy.

Hyaluronic acid (HA) products have been used successfully for years to treat joint disease in the horse. It is recognized that hyaluronic acid therapy:

- Decreases synovial fluid inflammatory mediators
- Decreases damage to articular cartilage
- Stimulates production of healthy joint fluid

Healthy joint.



"I could give you all kinds of reasons why I've come to trust Legend over the years. But there's one that really stands out: It works."

– BOB BAFFERT

3-time Eclipse Award winning Thoroughbred trainer

Why Legend® (hyaluronate sodium) Injectable Solution is an excellent choice for equine joint inflammation.



Legend is the joint disease therapy that helps stop acute damage before it becomes chronic.

Legend® (hyaluronate sodium) is pure hyaluronic acid, similar to the HA present in normal joint fluid. And, since its introduction nearly 10 years ago, Legend is still the only FDA-approved intravenous equine joint therapy.

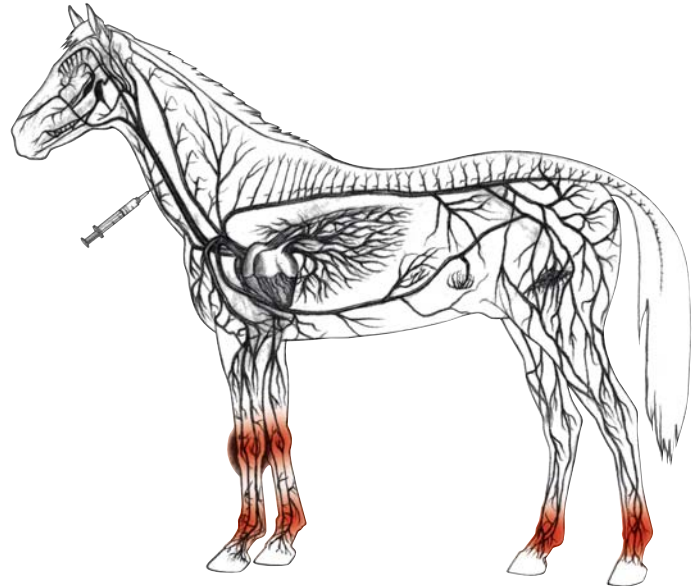
Legend offers a choice of administration.

- Intravenous (I.V.) for convenience and ease of use.
 - No joint preparation required
 - Time-saving administration technique
 - Beneficial therapy for multiple joint sites
- Intra-articular for individual joint therapy.

Legend is pure, safe and reliable.

A patented biological fermentation process produces highly purified HA—the only hyaluronic acid approved by the FDA for I.V. administration.

- No foreign protein
- Reduced risk of reactions
- High standards of quality control



Available exclusively from veterinarians, Legend is the first and only equine joint therapy FDA-approved for intravenous (I.V.) administration.

"FDA approval means a company has jumped over some tough obstacles to have a product tested and proven to be effective.

Why would I want a product for my horses that offers anything less?"

– BOB AVILA

Named Greatest Horseman in 2000

by the National Reined Cow Horse Association

Legend® (hyaluronate sodium) is backed by research.

A Colorado State University study¹ demonstrated an I.V. administration of Legend® (hyaluronate sodium):

- Significantly decreased inflammation associated with joint disease in the horse.
- Decreased inflammatory mediators within the joint.
- Decreased the degree of lameness in horses with arthritis (joint inflammation).

The one trusted throughout the industry.

Legend is the first choice of more equine veterinarians for the treatment of equine joint inflammation.² And it is the *only* I.V. equine joint therapy backed by research, safety testing and the unequaled support of Bayer.

Safety in breeding animals has not been determined.

Nothing is proven to work better than Legend.

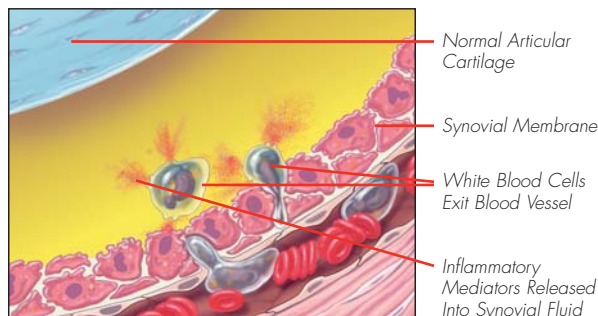
In well-controlled clinical field trials, the overall improvement was rated as excellent or good in more than 90% of all horses treated with Legend intravenously or intra-articularly.³

¹ Kawcak CE, Frisbie DD, Trotter GW, McIlwraith CW, Gillette SM, Powers BE, Walton, RM: Effects of intravenous administration of hyaluronate sodium on carpal joints in exercising horse after arthroscopic surgery and osteochondral fragmentation. *AJVR* Vol. 58, No. 10, October 1997.

² Independent survey. Data on file.

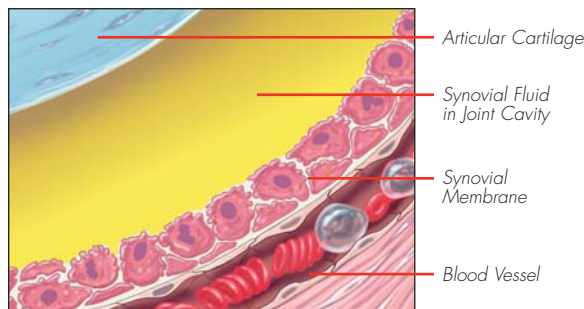
³ Freedom of Information Summary for Legend® (hyaluronate sodium) Injectable Solution.

Damaged joint.



Legend significantly decreases inflammation to help return the joint to normal function.

Normal joint.



The only FDA-approved I.V. joint therapy.

With an FDA-approved product, such as Legend, you are assured of some clear-cut advantages.

- Stringent standards for quality, consistency and safety have been met.
- The manufacturing facility is FDA-approved, with quality controls to ensure strength, identity, purity and potency.
- Rigorous monitoring is done on a regular basis, according to FDA requirements for safety, efficacy and side effects.

"It's extraordinary to find this kind of commitment. Legend earned our respect as an equine joint therapy; then, we discovered how much Bayer does to support the entire equine profession."

—DAVID & KAREN O'CONNOR
Olympic equestrian champions

Bayer shares your love of horses and supports the equine profession.

Bayer's tradition of supporting equine veterinary care extends decades into the past, and stretches well into the future. Here are just a few of the ways Bayer provides support and goodwill for horses, their owners, trainers and veterinarians.



Bayer is a major sponsor of the United States Equestrian Team, and the Official Horse Health Care Manufacturer for USET.



Bayer is the oldest existing sponsor of the American Quarter Horse Association.



In a joint effort with the American Association of Equine Practitioners, Bayer established The Equine Connection,[™] National AAEP Locator (www.getadv.com), an online service to help horse owners locate an equine veterinarian anywhere in the USA. Bayer also publishes a series of AAEP client education brochures.

*For more information
call Bayer Customer Service at 1-800-633-3796.*

Legend is the #1 choice of veterinarians.2

Legend[®] (hyaluronate sodium)

Injectable Solution

For Intravenous Or Intra-Articular Use In Horses Only

CAUTION:

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

Legend[®] (hyaluronate sodium) Injectable Solution is a clear, colorless solution of low viscosity. Legend Injectable Solution is pyrogen free, sterile and does not contain a preservative. It is administered by intravenous or intra-articular injection.

Hyaluronic acid, the conjugate acid of hyaluronate sodium, is extracted from the capsule of *Streptococcus* spp. and purified, resulting in a form which is essentially free of protein and nucleic acids.

Legend Injectable Solution is supplied in 2 mL (20 mg) and 4 mL (40 mg) vials. Each mL contains 10 mg hyaluronate sodium, 8.5 mg sodium chloride, 0.223 mg sodium phosphate dibasic and 0.04 mg sodium phosphate monobasic. The pH is adjusted to between 6.5 and 8.0 with sodium hydroxide or hydrochloric acid.

CHEMISTRY:

Hyaluronic acid, a glycosaminoglycan, can exist in the following forms depending upon the chemical environment in which it is found: as the acid, hyaluronic acid; as the sodium salt, sodium hyaluronate (hyaluronate sodium); or as the hyaluronate anion. These terms may be used interchangeably but in all cases, reference is made to the glycosaminoglycan composed of repeating subunits of D-glucuronic acid and N-acetyl-D-glucosamine linked together by glycosidic bonds. Since this product originates from a microbial source, there is no potential for contamination with dermatan or chondroitin sulfate or any other glycosaminoglycan.

PHARMACOLOGY:

Hyaluronic acid is a naturally occurring substance present in connective tissue, skin, vitreous humour and the umbilical cord in all mammals. High concentrations of hyaluronic acid are also found in the synovial fluid. It also constitutes the major component of the capsule of certain microorganisms. The hyaluronic acid produced by bacteria is of the same structure and configuration as that found in mammals.

The actual mechanism of action for hyaluronate sodium in the healing of degenerative joint disease is not completely understood. One major function appears to be the regulation of normal cellular constituents. This effect decreases the impact of exudation, enzyme release and subsequent degradation of joint integrity. Additionally, hyaluronate sodium exerts an anti-inflammatory action by inhibiting the movement of granulocytes and macrophages.¹

Hyaluronate molecules are long chains which form a filter network interspersed with normal cellular fluids. It is widely accepted that injection directly into the joint pouch enhances the healing of inflamed synovium by restoring lubrication of the joint fluid. This further supplements the visco-elastic properties of normal joint fluid.

CONTRAINDICATIONS:

There are no known contraindications for the use of Legend[®] (hyaluronate sodium) Injectable Solution in horses.

TOXICOLOGY:

Legend Injectable Solution was administered to normal horses at one, three and five times the recommended intra-articular dosage of 20 mg and the intravenous dosage of 40 mg.

Treatments were given once weekly for nine consecutive weeks (three times the maximum duration). No systemic clinical signs were observed nor were there any adverse effects upon hematology or clinical chemistry parameters. A transient, slight to mild post-injection swelling of the joint capsule occurred in some of the animals treated intra-articularly with Legend Injectable Solution as it did in the saline treated control horses. No gross or histological lesions were observed in the soft tissues or the surface areas of the treated joint.

CLINICAL STUDIES:

Forty-six horses with lameness in either the carpal or fetlock joints were treated intravenously or intra-articularly with Legend Injectable Solution in a well controlled clinical field trial conducted at four locations. One, two or three injections were given based on clinical improvement. Overall clinical improvement was judged as excellent or good in 90% of the cases treated intravenously and 96% of those treated intra-articularly with Legend Injectable Solution.