Adequan, Legend, MAP-5, Acetyl-D-Glucosamine, Pentosan, Polyglycan...as a horse owner, you have probably heard these names a million times. You also probably recognized them as products that are used in the prevention and treatment of equine articular, or joint, diseases. Numerous articles and advertisements extol the virtue of dozens of different joint therapy products, but what do they really do? What product is the most appropriate for your horse? Joint medications and supplements are available in 4 main forms of delivery, namely intravenous (IV), intramuscular (IM), intraarticular (IA, i.e. in the joint) and oral. This article will discuss a few of the most commonly used injectable products. Keep posted for a discussion about oral products in a future newsletter! But first, a little background information about equine joint disease...

Your horse's joints are designed to flex, compress and extend hundreds of times per day while carrying his weight for years on end. Add a rider's weight and increase athletic demand, and some level of joint inflammation will result due to repeated trauma or stress to the joint. The definition of a joint is “the junction between two or more bones.” Joints have several components, including: collateral ligaments (which prevent the lateral or side to side movements of bones), synovial fluid (the fluid which fills the space between the bones and provides lubrication and nourishment to the cartilage), joint capsule (which stabilizes the joint and contains all the structures of the joint), synovial membrane (the inner lining of the joint capsule which produces and regulates the synovial fluid), and articular cartilage (the soft structural tissue that covers and cushions the ends of the bones where they meet to make up the joint). The cartilage is a framework of tissue composed of collagen fibers, which give the structure its strength. The collagen is interlaced with proteoglycans, which are long, protein-based molecules with multiple attached glycosaminoglycan (GAG) chains that trap water within its matrix. As a joint flexes, the cartilage compresses and expands, forcing water in and out of its collagen matrix to provide a shock absorbing effect.

The term “arthritis,” or inflammation of a joint, can be used to describe any spectrum of joint disease ranging from early, mild, barely detectable soft tissue inflammation within the joint to chronic, severe, crippling cartilage degeneration and bone spurring. Traumatic joint disease in horses includes synovitis (inflammation of the fluid producing synovial membrane), capsulitis (inflammation of the fibrous joint capsule) and osteoarthritis (degeneration of the articular cartilage and underlying subchondral bone). In many cases, every day repetitive microtrauma produces minute damage within the joint structures that triggers mild inflammatory responses to make repairs. Normally, the body’s own defenses control inflammation and the joint remains healthy and sound.
Sometimes, however, the rate of degeneration exceeds the rate of regeneration and arthritis begins to develop. If the inflammatory process overwhelms the body’s ability to contain it, either from a single acute injury or from many years of use, a cascade of events ensues: inflammatory enzymes break down the thick, slippery lubricating synovial fluid, which becomes thin and watery. Proteoglycans are lost and collagen fibers lose structure, diminishing the cartilage’s ability to retain lubricating water. The cartilage becomes eroded or cracked, and this damage stimulates even more inflammation. The joint capsule fills with more watery fluid, leading to pressure, pain and stiffness. The cascade of inflammation leads to a buildup of more inflammatory enzymes that further degrade the synovial fluid and cartilage. Left un-checked, this inflammatory cycle can continue until eventually the cartilage tears or erodes away entirely, leaving the exposed ends of the bones to rub against each other.

It is not possible to cure arthritis at this time, but appropriate treatment can halt or slow the inflammatory cycle that results in permanent or progressive joint damage. The key is early identification of joint inflammation, ideally before any cartilage damage has occurred. Truthfully, most joint supplements do far more to prevent inflammation and joint damage than they do to treat it once it has started. Once marked inflammation has taken hold within a joint (resulting in radiographic changes and the clinical signs of lameness, stiffness, joint swelling, poor performance, etc.) direct treatment of the joint with intra-articular injections (“joint injections”) is often indicated. Your veterinarian will decide if it is most appropriate to begin therapy with either intramuscular and/or intravenous joint therapy, intra-articular joint therapy, or all of the above.

So what joint therapy product would be the most appropriate for YOUR horse? First, let’s talk a little more about articular cartilage. Think of cartilage as a tree...the roots, trunk and branches can all be represented by GAG’s (i.e. hyaluronan/hyaluronic acid, glucosamine, chondroitin). It would seem intuitive to treat or supplement a horse with components such as hyaluronic acid, glucosamine and chondroitin, the building blocks of articular cartilage. Unfortunately, it’s not that simple. If a tree falls down (analogous to cartilage being damaged), simply throwing pieces of tree on top of the fallen trunk will not make the tree regrow. So what are all these joint therapy products designed to do!? These products mainly function as anti-inflammatory agents. Inflammation is governed by hundreds of different chemical mediators. The ability of any given joint therapy product to work depends largely on whether or not the inflammation the horse is experiencing is mediated by the particular set of inflammatory mediators that the product targets. This is why one product works fabulously in one horse, but not in another. It is not possible to positively identify the exact inflammatory mediators occurring in each and every horse, therefore multiple product trials are often necessary to pinpoint the most effective joint therapy product for your horse. That being said, who are the major players in IV and IM joint therapy products?

First, a little background about the types of products commonly used for IV or IM joint therapy...in general, these products are categorized as either FDA-approved innovator drugs, FDA-approved generic drugs, medical devices or compounded products. It can take years and millions of dollars to get an FDA-approved innovator drug from the laboratory to the marketplace, and the manufacturers of an FDA-approved product must continually ensure its consistency, efficacy and good manufacturing practices/safety. An FDA-approved product must contain a package insert.
that explains specifically where the drug should be administered, what the dosage should be for a specific species and what conditions the drug is supposed to treat. It is also mandatory of any manufacturer of an FDA-approved product to notify the FDA with any adverse reactions to their product.

According to the FDA, a generic drug is bioequivalent to the innovator drug, is also FDA-approved, and the manufacturer must scientifically prove the generic drug performs in the same manner as the innovator drug. The generic drug manufacturer must comply with the same regulations as the innovator drug and it must have a product insert. Not every innovator drug has a generic brand available to the market. For example as we will discuss below, Adequan has no generic equivalent. On the other hand, Legend’s generic equivalent is NexHA.

A medical device is defined by the FDA as an instrument, machine or implement that can be used to diagnose, cure or prevent a disease, which does not achieve its intended action through chemical reaction or being metabolized by the body. Simply stated, a medical device was not designed to be absorbed by the body to achieve its purpose. A medical device is not approved by or registered with the FDA. A medical device cannot be marketed as a drug or claim to work like one. Several medical devices that are used “extra label” as joint therapy products are designed to be wound washes, surgical joint lavages or cell culture fluids.

Compounded products are available to veterinarians to treat a unique disease or address a unique situation, and should be reserved for when there isn’t a commercially available FDA-approved product to treat that specific condition. The compounded product must be made for a specific patient to accommodate a specific need at a specific point in time. Compounded products can vary greatly in their chemical makeup and are not regulated for sterility and safety as stringently as FDA-approved products, therefore it is extremely important to utilize a reputable compounding pharmacy.

Back to the major players in products used for joint therapy…let’s start with the products that are FDA-approved to treat joint dysfunction in the horse. Adequan i.m. is an FDA-approved innovator drug with no generic bioequivalent. It is the only product approved by the FDA for the intramuscular treatment of non-infectious joint disease in the horse. Adequan is a polysulfated glycosaminoglycan (PSGAG), prepared by extracting gycosaminoglycans (GAGs) from bovine tracheal cartilage, a naturally occurring complex molecule that is an essential building block of the cartilage matrix. This PSGAG passes through the synovial membrane and is absorbed into the articular cartilage. Adequan inhibits harmful enzymes that attack the synovial fluid and cartilage, and stimulates cartilage repair by stimulating the chondrocytes (cartilage cells) to upregulate and produce the main components of articular cartilage. Adequan relieves pain caused by swelling and inflammation, restores synovial lubrication and halts the cartilage-damaging disease cycle. The correct labeled dose (for the average sized horse) is 500 mg (1 vial) every 4 days for 28 days (7 doses) in order to achieve a steady state of drug in the articular cartilage. This regime used to be called a “loading dose,” as it used to be recommended to administer 1 dose of Adequan monthly thereafter. Further studies by the manufacturer have since confirmed that Adequan is most effective at decreasing inflammation in joints when administered in a 7 dose/28 day regime 1-3 times per year rather than 1 dose per month. Anecdotally, I have observed that it is also useful to administer a single dose 48-72 hours prior to every competition or event.

Legend is also an FDA-approved innovator drug that is composed of pure hyaluronic acid (HA or hyaluronan). Unlike Adequan, Legend has a bioequivalent FDA-approved generic drug recently released on the market called NexHA. Both Legend and NexHA are the only drugs that are FDA-approved for the intravenous treatment of non-infectious joint disease (specifically synovitis) in the horse. HA is a naturally occurring substance present in connective tissue, skin, vitreous humor (eye liquid) and the umbilical cord of all mammals. High concentrations of HA are found in synovial fluid as it is produced by the synovial membrane and is responsible for the lubrication of the articular cartilage. Interestingly, it also constitutes the major component of certain micro-organisms. For example, the HA produced by the Streptococcus bacteria is of the same structure and configuration as that found in mammals. Legend and NexHA are extracted from the capsule of Streptococcus species and purified, resulting in a pure form of HA. The actual mechanism of action of HA in the healing of degenerative joint disease is not completely understood, but one major function appears to be the regulation of normal cellular constituents of the joint. This effect decreases the impact of enzymes that degrade joint integrity, thus relieving swelling, pain and inflammation. Additionally, HA exerts an anti-inflammatory action by inhibiting the movement of inflammatory white blood cells into the joint. The correct labeled dose (for the average sized horse) is 40 mg (1 vial) weekly for 3 weeks (3 doses), repeated 1-3 times per year. Similar to Adequan, anecdotally I have observed that it is also useful to administer a single dose 48-72 hours prior to every competition or event. It has been generally recognized that the two medications (Adequan and Legend/NexHA) administered in conjunction will have a much greater positive effect for your horse’s joints than if administered alone.

Another HA product that you may be familiar with is MAP-5. MAP-5 is also FDA-approved, however it is FDA-approved for use in the collection, handling, culture and cryopreservation of embryo, ova, sperm and other cells (it acts as a replacement for serum and serum products in cell handling and freezing). In regards to its “extra label” use as a joint therapy product, MAP-5 is considered to be a medical device and there have been no controlled studies about its safety, efficacy or optimal use.

Switching gears, let’s discuss Acetyl-D-Glucosamine, a product that is commonly referred to as “generic Adequan.” As previously stated, Adequan has no bioequivalent generic. Adequan is a polysulfated glucosaminoglycan, while Acetyl-D-Glucosamine is a monosaccharide derivative of glucose (a component of chitin found in fungi and many invertebrates, including crustaceans, insects and nematodes) and is chemically related to glucosamine, chondroitin and hyaluronic acid. In other words, they are not even close to the same chemical! One study has been performed comparing Acetyl-D-Glucosamine to Adequan, funded by Luitpold (the manufacturer of Adequan) and presented at the annual American Association of Equine Practitioners (AAEP) conference in 2004. This study found Acetyl-D-Glucosamine not to be as effective as Adequan at the conventional dosage and treatment level. The author of the study said that while products such as Acetyl-D-Glucosamine are “likely” to have a “positive effect on injured or diseased equine joints,” the work has not been done to determine appropriate dose or treatment regime. Acetyl-D-Glucosamine is not an FDA-approved product and must be manufactured for each specific patient on a case by case basis by a compounding pharmacy. It can be compounded in multiple different strengths and is generally administered intramuscularly in various amounts at various intervals. At this date and time, similar to the findings of the Luitpold-funded study in 2004, the work has not been done to determine appropriate
product from a reputable pharmacy. The bottom line is to treat joint inflammation early or preferably, to prevent it from occurring entirely!

If the results that you achieve are suboptimal, work with your veterinarian to select a different product to use either in an “extra label” manner or a compounded product from a reputable pharmacy. The latter could beneficially influence cartilage structure and alleviate arthritis.

The “new kid on the block” in terms of joint therapy products is Sodium Pentosan Polysulfate (PPS), a polymer produced from xylan, a complex hemicellulose extract from the beech wood plant. In the United States, PPS is marketed under the name Pentosan and is FDA-approved as a post-surgical joint lavage. PPS is cleared for distribution by the Australian equivalent of the FDA as a product called PentAussie, which is a combination of PPS and an injectable form of glucosamine (note: the concentration of PPS contained within PentAussie is half that contained in Pentosan). PPS affects arthritic joints in several ways...PPS stimulates the synthesis of proteoglycans and increases the amount of these substances incorporated back into the cartilage matrix, stimulates the joint capsule to produce increased amounts of lubricating hyaluronic acid in the synovial fluid, inhibits and modulates inflammatory mediators within the joints, and breaks up fibrin (small blood clots) to optimize the nourishing subchondral bone blood supply to the cartilage bed. Adverse effects of PPS are related to its function as an anticoagulant or thrombolytic agent...it’s not recommended for use in post-surgical cases, for horses with autoimmune problems, prior bleeding issues or in situations in which trauma and possible bleeding could occur. These concerns bring the two aspects of PPS into conflict, since the typical situation in which osteoarthritis becomes a problem requiring treatment is in performance sport horses, yet it’s exactly this use that’s most likely to result in possible trauma, injury and bleeding. This was the dilemma that, at least in part, initially prevented more widespread use of PPS in athletic horses. Attention to dosage and frequency resulted in relatively safe use over time, however, and veterinarians and trainers in Australia and Europe became comfortable with its use. PPS was routinely used in racehorses throughout those regions, with no documented increase in problems associated with exercise-induced pulmonary hemorrhage or other performance-related bleeding problems. In the United States, PPS is most commonly administered either in an “extra label” manner or as a compounded product via an intramuscular injection every 5-7 days for 4-5 doses. Overall, both laboratory research and owner testimonials indicate that PPS does combat joint inflammation and improve performance.

Lastly, Polyglycan is a patented formulation of hyaluronic acid, sodium chondroitin sulfate and N-acetyl-D-glucosamine, FDA-approved for post-surgical lavage of synovial compartments. As you now know, this means that it is a medical device and its use as an injectable joint therapy product is “extra label.” Polyglycan has been off-handedly referred to as “generic Adequan and Legend,” but of course that is not correct. In 2007 Luitpold, the manufacturers of Adequan, performed a study on 16 horses to compare Adequan and Polyglycan. Eight horses were administered Adequan injections IM and eight horses received Polyglycan injection IV. All of these horses were injected with a chemical to induce inflammation in the knee joint. Results indicated that 88% of the horses administered Adequan had less lameness while only 50% of the horses administered Polyglycan had less lameness; 48% of the Adequan horses had reduced joint swelling while none of the Polyglycan horses had reduced swelling; 98% of the Adequan horses demonstrated stride length recovery vs. 61% of the Polyglycan horses; and 95% of the Adequan horses regained normal knee range of motion vs. 61% of the Polyglycan horses. The results would suggest that while there is some positive effect to administering Polyglycan, Adequan is a more effective joint therapy product.

When considering a treatment option for your horse, it is important to be educated about what the product you are planning to use is designed and proven to do. All of these products are used with the common goal of returning an abnormal joint environment back to healthy homeostasis. From a practitioner’s point of view, I always prefer to administer an FDA-approved drug that has been proven to treat joint dysfunction, monitored for safety, and quality assured. The first joint therapy product(s) that I choose is/are directed by my clinical findings through a lameness evaluation, flexion tests, radiographs, ultrasound, etc. (or sometimes I decide that it would be most beneficial to start directly with intra-articular injections, and add an IM or IV product as an adjunctive treatment). That being said, recall that inflammation is governed by hundreds of chemical mediators and that the ability of any given product to work depends on the inflammatory mediators experienced by YOUR horse. Be aware that it may take trial and error to find the most effective joint therapy product for each horse. Begin by treating with a product that is FDA-approved to treat joint disease...it is the safest option for your horse and carries the greatest likelihood of success. If the results that you achieve are suboptimal, work with your veterinarian to select a different product to use either in an “extra label” manner or a compounded product from a reputable pharmacy. The bottom line is to treat joint inflammation early or preferably, to prevent it from occurring entirely!

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