TECHNICAL BULLETIN

The Difference is in the Details:
FDA Approved Drugs vs. Compounded Products and Veterinary Medical Devices
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Equine veterinarians are increasingly challenged to provide sound medical care while operating within economic restrictions. In efforts to maintain client goodwill and minimize treatment costs, veterinarians may consider non-Food and Drug Administration (FDA) approved product alternatives, such as compounded drugs and veterinary medical devices. When veterinarians choose to administer products that have not undergone equivalent clinical testing for safety and efficacy in the horse, unforeseen risks may arise. Therefore, it is important for veterinarians to understand and, if appropriate, communicate the importance of using FDA approved drugs, such as Adequan® i.m. (polysulfated glycosaminoglycan) and BetaVet® (betamethasone sodium phosphate & betamethasone acetate injectable suspension).

Adequan® i.m. and BetaVet® are FDA Approved Pioneer Drugs.

FDA Pioneer Drug:¹

• A drug that has undergone the scrutiny of blinded controlled studies to demonstrate safety and efficacy in accordance with Good Laboratory Procedures (GLPs)
• The product is manufactured under FDA mandated Good Manufacturing Practices (GMPs) in regularly inspected plants

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Adequan® i.m.

INDICATIONS
For the intramuscular treatment of non-infectious degenerative and/or traumatic joint dysfunction and associated lameness of the carpal and hock joints in horses.

IMPORTANT SAFETY INFORMATION

There are no known contraindications to the use of intramuscular Adequan® i.m. brand Polysulfated Glycosaminoglycan in horses. Studies have not been conducted to establish safety in breeding horses. WARNING: Do not use in horses intended for human consumption. Not for use in humans. Keep this and all medications out of the reach of children. CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

¹FDA Pioneer Drug: A drug that has undergone the scrutiny of blinded controlled studies to demonstrate safety and efficacy in accordance with Good Laboratory Procedures (GLPs), and the product is manufactured under FDA mandated Good Manufacturing Practices (GMPs) in regularly inspected plants.
INDICATION: BetaVet® is indicated for the control of pain and inflammation associated with osteoarthritis in horses.

SELECTED SAFETY INFORMATION
For Intra-Articular (I.A.) Use in Horses.

CONTRAINDICATIONS: BetaVet® is contraindicated in horses with hypersensitivity to betamethasone. Intra-articular injection of corticosteroids for local effect is contraindicated in the presence of septic arthritis.
What about Compounded Veterinary Drugs?

Compounded Drug:¹

- Any drug manipulated to produce a dosage form (other than that provided for in the directions for use on labeling of the approved drug product)
- Compounded drugs are not ‘generic’ drugs
- Neither cost nor convenience is a justification for using compounded preparations. Compounding provides a customized formulation for the special needs of a particular patient, when no approved presentation is available, within the context of a Veterinarian-Client-Patient Relationship (VCPR)
- FDA-approved medications should be used to formulate compounded medications
- Some state pharmacy boards require compounded drugs to be dispensed at cost
- Every compounded drug must have a beyond-use date which should not exceed 180 days from preparation³
- The prescribing veterinarian assumes responsibility when using compounded preparations
- How to identify:
  - The primary label of a compounded medication should include a statement notifying the client that the medication has been compounded. When a branded drug product has been used as a source of the drug, the generic name of the drug product, not the proprietary name, should be placed on the label¹
  - State regulations differ in label requirements

WARNINGS: Do not use in horses intended for human consumption. Clinical and experimental data have demonstrated that corticosteroids administered orally or parenterally to animals may induce the first stage of parturition when administered during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta, and metritis. Additionally, corticosteroids administered to dogs, rabbits and rodents during pregnancy have resulted in cleft palate in offspring and in other congenital anomalies including deformed forelegs, phocomelia and anasarca. Therefore, before use of corticosteroids in pregnant animals, the possible benefits to the pregnant animal should be weighed against potential hazards to its developing embryo or fetus. **Human Warnings:** Not for use in humans. For use in animals only. Keep this and all medications out of the reach of children. Consult a physician in the case of accidental human exposure.
Are Veterinary Medical Devices Equivalent to FDA Approved Drugs?

Veterinary Medical Devices:

- Medical devices as defined by the FDA in the Food Drug and Cosmetic Act, Section 210(h): “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent,…which does not achieve any of its principal intended purposes through chemical action… and is not dependent upon being metabolized for the achievement of any of its principal intended purposes”
- Although under FDA oversight for promotion and marketing, devices manufactured solely for use in veterinary medicine are not required to undergo a pre-marketing approval process
- The manufacturing process of veterinary devices is not required to meet uniform standards, i.e. no set standards to assure quality control for purity, potency, stability and sterility; no mandatory requirements for reporting adverse events
- “Off-label” drug use does not apply to veterinary medical devices. These devices have not undergone clinical testing for safety or efficacy as a drug, hence no approved label Indication, Dosing, or Contraindication information
  - A 2016 study evaluated the efficacy of IV administration of a combination product containing hyaluronan, sodium chondroitin sulfate, and N-acetyl-D-glucosamine for prevention or treatment of osteoarthritis in 32 healthy 2- to 5- year old horses
  - The study concluded that caution should be used when administering the product IV to horses, particularly when administering it prophylactically, as it may have no benefit or may even cause harm

BetaVet®

SELECTED SAFETY INFORMATION

PRECAUTIONS: Corticosteroids, including BetaVet®, administered intra-articularly are systemically absorbed. Do not use in horses with acute infections. Acute moderate to severe exacerbation of pain, further loss of joint motion, fever, or malaise within several days following intra-articular injection may indicate a septic process. Because of the anti-inflammatory action of corticosteroids, signs of infection in the treated joint may be masked. Due to the potential for exacerbation of clinical signs of laminitis, glucocorticoids should be used with caution in horses with a history of laminitis, or horses otherwise at a higher risk for laminitis. Use with caution in horses with chronic nephritis, equine pituitary pars intermedia dysfunction (PPID), and congestive heart failure. Concurrent use of other anti-inflammatory drugs, such as NSAIDs or other corticosteroids, should be approached with caution. Due to the potential for systemic exposure, concomitant use of NSAIDs and corticosteroids may increase the risk of gastrointestinal, renal, and other toxicity. Consider appropriate wash out times prior to administering additional NSAIDs or corticosteroids.
Veterinary device labeling and ingredients may appear very similar to FDA approved drugs
- For example, some products contain only monosulfated chondroitin sulfate, which is not chemically equivalent to polysulfated glycosaminoglycan (PSGAG) in Adequan®. Adequan® contains 3-4 sulfate esters per disaccharide molecule, differs in structure and function, and no bioequivalent product exists6,7

How to identify:
- The labeling of medical devices used within veterinary medicine may not contain language identifying the product as a device. If the practitioner has questions regarding the status of a product, he or she should contact the manufacturer

In summary, the significance of FDA approval is essential for both veterinarians and clients to understand. For a new drug to satisfy each stage of the FDA approval process often takes years, and veterinarians should consider the benefits of using these drugs over non-approved alternatives. Stringent FDA approval requirements provide the benchmark for veterinary drug safety and efficacy, and allow practitioners to provide optimal care to the horse.

References:

ADVERSE REACTIONS: Adverse reactions reported during a field study of 239 horses of various breeds which had been administered either BetaVet® (n=119) or a saline control (n=120) at five percent (5%) and above were: acute joint effusion and/or local injection site swelling (within 2 days of injection), 15% BetaVet® and 13% saline control; increased lameness (within the first 5 days), 6.7% BetaVet® and 8.3% saline control; loose stool, 5.9% BetaVet® and 8.3% saline control; increased heat in joint, 2.5% BetaVet® and 5% saline control; and depression, 5.9% BetaVet® and 1.6% saline control.

DOSAGE AND ADMINISTRATION: Shake well immediately before use. Use immediately after opening, then discard any remaining contents.

RX ONLY
American Regent Animal Health is proud to provide the equine industry with the following Food and Drug Administration (FDA) approved products:

To report an adverse event for any American Regent Animal Health product:

- Contact American Regent Animal Health
  - Toll-free: (800) 734-9236
  - Email: pv@americanregent.com

- Contact the Center for Veterinary Medicine
  - Call: (888) FDA-VETS
  - Email: AskCVM@fda.hhs.gov

Please see accompanying Full Prescribing Information or at www.adequan.com.
**Adequan® i.m. SINGLE DOSE**

**Brand of Polysulfated Glycosaminoglycan (PSGAG)**

Solution 500 mg/5 mL
For Intramuscular Use In Horses

**DESCRIPTION:** Each milliliter of Adequan® i.m. contains 500 mg of Polysulfated Glycosaminoglycan and Water for Injection q.s. Sodium Hydroxide and/or Hydrochloric Acid added when necessary to adjust pH. Sodium Chloride may be added to adjust tonicity.

**PHARMACOLOGY:** Polysulfated Glycosaminoglycan is chemically similar to the glycosaminoglycans in articular cartilage matrix. PSGAG is a potent proteolytic enzyme inhibitor and diminishes or reverses the pathologic processes of traumatic or degenerative joint disease which result in a net loss of cartilage matrix components. PSGAG improves joint function by reducing synovial fluid protein levels and increasing synovial fluid hyaluronic acid concentration in traumatized equine carpals and hock joints.

**INDICATIONS:** Adequan® i.m. is recommended for the intramuscular treatment of non-infectious degenerative and/or traumatic joint dysfunction and associated lameness of the carpals and hock joints in horses.

**DOSE AND ADMINISTRATION:** The recommended dose of Adequan® i.m. in horses is 500 mg every 4 days for 28 days intramuscularly. The injection site must be thoroughly cleansed prior to injection. Do not mix Adequan® i.m. with other drugs or solvents.

**CONTRAINDICATIONS:** There are no known contraindications to the use of intramuscular Polysulfated Glycosaminoglycan.

**WARNINGS:** Do not use in horses intended for human consumption. Not for use in humans. Keep this and all medications out of the reach of children.

**PRECAUTIONS:** The safe use of Adequan® i.m. in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated.

**ANIMAL SAFETY:** Toxicity studies were conducted in horses. Doses as high as 2,500 mg were administered intramuscularly to 6 horses twice a week for 12 weeks. This dosage is 5 times the recommended dosage and 3 times the recommended therapeutic regimen. Clinical observations revealed no soreness or swelling at the injection site or in the affected joint. No animal had any clinical or laboratory evidence of toxicity.

**STORAGE CONDITIONS:** Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) (See USP Controlled Room Temperature). Discard unused portion. Dispose of spent needles in accordance with all federal, state and local environmental laws.

**HOW SUPPLIED:** Adequan® i.m. solution, 500 mg/5 mL (100 mg/mL) in a 5 mL single dose glass vial.

NDC 10797-995-70 5 mL Single Dose Vials Packaged 7 vials per box

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NADA #140-901, Approved by FDA

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**Adequan® i.m. MULTI-DOSE**

**Brand of Polysulfated Glycosaminoglycan (PSGAG)**

Solution 100 mg/mL in a 50 mL Preserved Multi-Dose Vial
For Intramuscular Use In Horses Only. Not for Intra-Articular Use.

**DESCRIPTION:** Each mL contains Polysulfated Glycosaminoglycan 100 mg, Benzyl Alcohol 0.9% w/v as a preservative, and Water for Injection q.s. Sodium Hydroxide and/or Hydrochloric Acid added when necessary to adjust pH. The solution is clear, colorless to slightly yellow.

**PHARMACOLOGY:** Polysulfated Glycosaminoglycan is chemically similar to the glycosaminoglycans in articular cartilage matrix. PSGAG is a potent proteolytic enzyme inhibitor and diminishes or reverses the pathologic processes of traumatic or degenerative joint disease which result in a net loss of cartilage matrix components. PSGAG improves joint function by reducing synovial fluid protein levels and increasing synovial fluid hyaluronic acid concentration in traumatized equine carpals and hock joints.

**INDICATIONS:** Adequan® i.m. Multi-Dose is recommended for the intramuscular treatment of non-infectious degenerative and/or traumatic joint dysfunction and associated lameness of the carpals and hock joints in horses.

**DOSE AND ADMINISTRATION:** Practice aseptic techniques in withdrawing each dose to decrease the possibility of post-injection bacterial infections. Adequately clean and disinfect the stopper prior to entry with a sterile needle and syringe. Use only sterile needles, and use each needle only once.

The vial stopper may be punctured a maximum of 10 times.

The recommended dose of Adequan® i.m. Multi-Dose in horses is 500 mg every 4 days for 28 days intramuscularly. The injection site must be thoroughly cleansed prior to injection. Do not mix Adequan® i.m. Multi-Dose with other drugs or solvents.

**CONTRAINDICATIONS:** There are no known contraindications to the use of intramuscular Polysulfated Glycosaminoglycan.

**WARNINGS:** Do not use in horses intended for human consumption. Not for use in humans. Keep this and all medications out of the reach of children.

**PRECAUTIONS:** The safe use of Adequan® i.m. Multi-Dose in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated.

**SAFETY AND EFFICACY:** Safety and efficacy studies utilizing Adequan® i.m. Multi-Dose were not performed. Adequan® i.m. Multi-Dose was approved based on the conclusion that the safety and effectiveness of Adequan® i.m. Multi-Dose will not differ from that demonstrated for the original formulation of Adequan® i.m.

**ANIMAL SAFETY:** Animal Safety studies utilizing Adequan® i.m. Multi-Dose were not performed. Safety studies were conducted in horses using the single dose formulation. Doses as high as 2,500 mg were administered intramuscularly to 6 horses twice a week for 12 weeks. This dosage is 5 times the recommended dosage and 3 times the recommended therapeutic regimen. Clinical observations revealed no soreness or swelling at the injection site or in the affected joint. No animal had any clinical or laboratory evidence of toxicity.

**STORAGE CONDITIONS:** Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) (See USP Controlled Room Temperature). Avoid prolonged exposure to temperatures ≥40°C (104°F). Use within 28 days of first puncture and puncture a maximum of 10 times. Dispose of spent needles in accordance with all federal, state and local environmental laws.

**HOW SUPPLIED:** Adequan® i.m. Multi-Dose solution, 5,000 mg/50 mL (100 mg/mL) in 50 mL multi-dose glass vials.

NDC 10797-959-01 50 mL Multi-Dose Vials Packaged 1 vial per box

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