Veterinary Technical Bulletin
April 20, 2020

1. Medroxyprogesterone (MPA)

The administration of medroxyprogesterone (once available as Depo-Provera) to horses has been associated with adverse events including anaphylactic reactions and sudden death. The United States Equestrian Federation established MPA as a prohibited substance as of December 1, 2019 (https://www.usef.org/media/press-releases/usef-board-of-directors-prohibits-use-of).

In 2019, the American Association of Equine Practitioners issued the following statement in regarding the use of MPA in competition horses:

> *Medroxyprogesterone acetate (MPA) is a synthetic progestin hormone administered to mares off-label in an attempt to suppress behavioral estrus. However, a controlled research study found that MPA was not effective at suppression of behavioral estrus. (1) Many veterinarians believe MPA modifies behavior by producing a calming effect in the horse and does not have a therapeutic benefit that goes beyond this behavior modification. Therefore, the AAEP recommends that MPA should not be administered to horses in competition.*
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> Gee EK, C DeLuca, JL Stylski, PM McCue. Efficacy of medroxyprogesterone acetate in suppression of estrus in cycling mares. J Equine Vet Sci 2009;29:140-145.

In consideration of the following:

1) Altrenogest (Regumate) has FDA-approval for use in the suppression of estrus and its use is permitted in fillies and mares in training and racing,
2) there is no evidence for efficacy of MPA in suppressing estrus,
3) there is no indication for the administration of MPA as a therapeutic medication,
4) there is evidence for risk to horses in the administration of MPA.

The RMTC recommends that MPA not be used.

2. Updates to the Uniform Classification of Foreign Substances

The Uniform Classification of Foreign Substances document is referred to by regulators in making penalty determinations in medication violation cases. The current version of the document in its entirety can be found at: https://drive.google.com/file/d/1F_bfqctaZJ2e95tPKCzqdh7Lz1nVjbff/view.

Changes recommended by the RMTC Board of Directors and approved by the ARCI follow:

Acetylcysteine has conventional use in racehorses as a mucolytic agent. Its acts by disrupting the disulfide bonds in mucin and results in decreased viscosity in mucus. Empirical evidence for its efficacy is lacking, as noted in the ACVIM Consensus Statement on Inflammatory Airway Disease of Horses. It is available in FDA-approved formulations for oral, inhalation, or injectable use. It is also available from compounding pharmacies. Other mucolytics (e.g. guaifenesin) having FDA-approval are assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. Mucolytics lacking FDA-approval (e.g. dembrexine and bromhexine) are assigned 4/B. Acetylcysteine has been added to the document and assigned a classification of 4/C consistent with other mucolytics having FDA-approval.

Altrenogest is a synthetic progestogen with FDA approval for the suppression of estrus in mares. Off-label use has included short-term administrations to intact males to suppress reproductive behavior. There is also an undocumented concern that altrenogest exerts an anabolic effect. The use of altrenogest is currently prohibited in geldings, stallions, and ridglings engaged in training and racing. Spayed mares have been added to the list of horses in which altrenogest is prohibited.

Bisphosphonates (BPs) are a class of drug that inactivate osteoclasts, the cell type that is responsible for removing damaged bone. Within this class of drug there are two sub-types, nitrogenous and non-nitrogenous, with the nitrogenous type having potency orders of magnitude greater than the non-nitrogenous. There are two non-nitrogenous BP products with FDA approval for use in the horse: Tildren (tiludronate sodium) and OsPhos (clodronate). These products carry label indications for use in the treatment of navicular disease in horses 4 years of age and older.

BP administration results in analgesia of unknown extent and duration. Concerns have been raised about the potential for BPs to impede or prevent bone adaptation to high-speed exercise when administered to young horses in race training. Failure to adapt and remodel in response to the biomechanical forces of high-speed exercise is associated with increased risk of fatal fracture. There is no data on the effect on bone of these substances in horses (of any age) engaged in high speed exercise and absent evidence for safety when used in these horses, the RMTC recommends their use only in accordance with label specifications. It is advisable to consult the local regulatory authority before administering Tildren or OsPhos as there may be additional requirements for their use such as pre-approval of treatments, treatment reporting/disclosure, and mandatory stand down periods. All bisphosphonates are assigned a classification of 3/A with no distinction made between nitrogenous and non-nitrogenous, and those with or without FDA approval.

Botulinum toxin is a neuromuscular blocking agent produced by the bacteria *Clostridium botulinum*. The toxin has conventional use in (human) cosmetic medicine in decreasing facial wrinkles and is also used to treat chronic migraine, spastic dysphonia, pathologic muscle contracture, and bladder dysfunction, among other conditions. Veterinary research has identified botulinum toxin as an adjunct in the treatment of laminitis, specifically in preventing rotation of the coffin bone when the boney laminae separate from the laminae of the hoof wall. A botulinum toxin product labelled for use in the horse in the treatment of laminitis is anticipated to receive FDA approval within the next 12-18 months. There are legitimate concerns about the off-label injection of this product and there is risk to horse safety and

welfare with improperly performed injections of this substance. A horse with laminitis will not be in training or entered to race. For this reason, there is no legitimate justification for botulinum toxin to be administered to a horse or in the possession of any individual at a facility under the jurisdiction of a racing regulatory authority. Botulinum toxin has been added to the document and assigned a classification of 2/A

Ethamsylate is an anti-thrombolytic agent. There are no ethamsylate-containing products that carry FDA approval. Ethamsylate exerts an effect similar to tranexamic acid (commonly known as Tran-X) and has been recognized by international racing regulatory authorities as a prohibited substance in the control of EIPH. Ethamsylate, a previously unclassified substance, has been detected in a post-race sample in a North American racing jurisdiction. Tranexamic acid, available in an FDA-approved formulation, is assigned a 4/C classification. Because of its similar effect but lack of FDA-approval, ethamsylate has been added to the document and assigned a classification of 4/B.

Selective Androgen Receptor Modulators (SARMs) are a class of drug that elicit an androgenic, anabolic effect. Within this class of drug, specific molecules can be developed to have differing ranges of anabolic and androgenic effects. SARMs have been used in human clinical trials, but no FDA-approved product exists. SARMs are on the World Anti-Doping Agency's Prohibited Substance list and are also included in the scope of substances regulated by the ARCI Model Rule on Out of Competition Testing. Specific examples of SARMs are andarine, ostarine, ligandrol, and testolone. Many other SARMs that are in varying stages of research and development have internal alpha-numeric designations (e.g. LG121071) and have not yet been assigned names. Therefore, it is necessary to assign a penalty classification to the drug class in its entirety. Consistent with anabolic agents lacking FDA approval, SARMs as a drug class, and andarine, ostarine, ligandrol, and testolone individually have been added to the document and assigned a 2/A classification.