



Veterinary Technical Bulletin

October 12, 2020

1. Ciclesonide

Ciclesonide is a glucocorticoid that is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances. Aservo EquiHaler™ (Boehringer-Ingelheim) received FDA-approval for the treatment of clinical signs associated with equine asthma, also known as Recurrent Airway Obstruction (RAO) and Summer Pasture Associated Pulmonary Disease (SPAOPD). The product is now commercially available by veterinary prescription.

Ciclesonide is a prodrug for the metabolically active des-ciclesonide. Following inhalation ciclesonide is converted to des-ciclesonide by cells in the lung epithelium.

Oral bioavailability is low (< 1%) and therapeutic concentrations are unlikely to be achieved via oral administration. Ciclesonide does not suppress serum cortisol concentrations and its use does not result in immunosuppression.

Ciclesonide is delivered intra-nasally by metered actuations of 343 mcg. Lavoie, et al. (Equine Veterinary Journal [2019] 51:779–786) determined that 2,744 mcg (8 actuations) delivered BID was the most effective dose in controlling experimentally induced equine asthma.

In order to provide guidance on the use of this product the RMTC Scientific Advisory Committee reviewed results from an administration study performed by Boehringer Ingelheim where horses were treated for ten days. Days 1-5 horses received 8 actuations BID. Days 6-10 horses received 12 actuations SID. Based on this dosing and treatment schedule, the data support a 48-hour **Detection Time**.

For more information, please refer to the RMTC's Ciclesonide Advisory (October 8, 2020).

2. Definitions:

Detection Time is the interval after a medication is administered during which it is detectable in a specific matrix (serum, plasma, urine, or hair) from any member(s) of a group of test horses. Detection times are determined from analysis of samples collected at specific time points following an administration of a medication to group of, potentially as few as 4, test horses.

For example, if a substance is detected in samples from 3 of 6 study horses at 24 hours post-administration, from 1 of 6 at 48 hours, and 0 of 6 at 72 hours, the Detection Time is 72 hours.

Detection times represent the foundation for a veterinarian to recommend a withdrawal interval that must also consider an owner's or trainer's risk aversion, the health of the individual horse to be treated, knowledge of the substance administered, other substances administered, and the potential for variability that could be expected to normally occur in a larger population.

The withdrawal interval used for a medication should always be longer than its detection time.

Restricted Administration Time (RAT) is a specified interval during which the treated horse cannot race, enter to race, or participate other regulated exercise as specified by a rule or regulation.

Restricted administration time enforcement can include surveillance, review of treatment reports or medical records, and out-of-competition testing, in addition to standard post-race testing. Evidence that a substance was administered during the restricted administration period establishes that a rule violation occurred. Restricted administration times may be associated with threshold concentrations in blood or urine and in those instances may have corresponding dosing specifications.

An example of a treatment controlled by a combination of RAT, threshold and dosing specifications is the administration of phenylbutazone (PBZ). Per ARCI Model Rules the administration of PBZ is prohibited at less than 48 hours to a horse's post time. The serum/plasma threshold of 0.3 mcg/mL provides analytical support for enforcement of the 48-hour RAT. The dosing specification for PBZ, single intravenous injection at 4.0 mg/kg, is the experimental dose that was used in developing the threshold.

Evidence that a horse was treated with PBZ at less than 48 hours, regardless of dose, route of administration (e.g. IV or oral), or concentration detected in a post-race sample, is sufficient to establish that the rule was violated.

Stand Down Period is a specified interval following a treatment during which the treated horse cannot race, enter to race, or participate other regulated exercise as defined by rule or regulation.

Stand down periods and restricted administration times accomplish essentially the same thing—a mandatory interval between a regulated treatment and a regulated event. Typically stand down periods refer to a period after treatment when the horse is prohibited from engaging in specified activities for a prescribed interval—e.g. the horse cannot train/enter/race for x days following treatment. Restricted administration times refer to an interval prior to a race—e.g. a specific treatment may not be administered within x days prior to a race.

An example of a stand down period is the ARCI's Model Rule on Prohibited Practices (4)(c) establishing that a horse having received Extra Corporeal Shock Wave treatment "...shall not be permitted to race or breeze for a minimum of 10 days following treatment."

Withdrawal Guidance is provided by regulators to assist licensees in complying with threshold-based regulations for controlled therapeutic medications.

Withdrawal guidance is a recommendation for a minimum interval between treatment and racing specific to the administration of a single medication, at a specified dose, route of administration (e.g. oral, intravenous, intra-articular, topical), and treatment schedule. It is typically formulated through statistical analysis performed on data from an administration study.

A longer withdrawal interval may be warranted in consideration of an individual horse's health or other factors (e.g. co-administration of other medications). The administration of a substance contrary to the withdrawal guidance does not, in and of itself, constitute a violation but may represent increased risk for a violation.

*As an example of how to use withdrawal guidance: A veterinarian has prescribed dantrolene capsules (Dantrium™) in a pre-race protocol for a horse with a history of tying up. The veterinarian selects a dose of 1,000 mg. Withdrawal guidance of 48 hours is provided for one 500 mg oral dose. In order to avoid risk of an overage the veterinarian recommends the 48-hour withdrawal interval be increased by one half-life, 4 hours**, to accommodate dosing at 2x that provided in the withdrawal guidance.*

** Knych, H.K., et al., *Pharmacokinetics and Metabolism of Dantrolene in Horses*, J. Vet Pharmacol. Therap., 2010; 34:238-246.