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Ciclesonide Advisory
October 12, 2020

Ciclesonide is a corticosteroid that is assigned 4/C in the ARCI's Uniform Classification of Foreign Substances, consistent with other corticosteroids. The ciclesonide-containing veterinary product 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). This veterinary prescription product became commercially available in the US in late September.

Ciclesonide, as Aservo Equihaler™, is administered by soft mist inhaler, a propellant-free medication delivery system. It is also available in formulations with FDA-approved formulations for human use and supplied in metered dose oral inhalers, pressurized cannisters that deliver a measured dose per each actuation.

Ciclesonide is a prodrug for des-ciclesonide. The enzymatic metabolism of the inactive ciclesonide to the pharmacologically active des-ciclesonide occurs in epithelial cells in the lungs. The administration of inhaled ciclesonide does not suppress serum cortisol concentrations nor does it exert an immunosuppressive effect. Ciclesonide is poorly absorbed following oral administration (< 1%), and therapeutic concentrations are unlikely to be achieved if ciclesonide is given orally.

Ciclesonide, as Aservo EquiHaler™ is delivered intra-nasally by metered actuations of 343 mcg. Lavoie, *et al.,* determined that 2,744 mcg (8 actuations) delivered twice daily was the most effective dose in controlling experimentally induced equine asthma[i].

The RMTC Scientific Advisory Committee (SAC) reviewed data from an administration study performed by Boehringer Ingelheim. In that study 12 horses were administered ciclesonide for 10 days. Days 1-5, horses received 2,744 mcg (8 actuations) twice daily. Days 6-10, horses received 4,116 mcg (12 actuations) once daily. Per label instructions, dosing is not weight-based; all horses received the same dose and treatment schedule.

Based on the data reviewed by the SAC, the **Detection Time*** for des-ciclesonide, dosed as ciclesonide and used as described in the above paragraph using Aservi Equihaler™, is 48 hours. This detection time is specific to ciclesonide administered as Aservo Equihaler™.

Extra-label, intra-nasal use in horses of human oral inhalers risks deposition of the drug in the horse's oropharynx; the route of administration then becomes both inhalation AND oral. The detection time for this combination of routes of administration is unknown.

Moreover, the Animal Medicinal Drug Use Act establishes that extra-label drug use (ELDU) is permitted only when "(t)here is no approved new animal or approved new human drug that, when used as labeled or in conformity with criteria established in this part, will, in the available dosage form and concentration, appropriately treat the condition diagnosed." Therefore, with the commercial availability of Aservo Equihaler™, ELDU of ciclesonide is not permitted.

* **Detection Time** is the first time point after a medication administration in which it is not detected 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 test horses.

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

Detection times enable a veterinarian to formulate a recommendation for 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 and any 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.

[i] Lavoie, JP, *et al., Effect of different doses of inhaled ciclesonide on lung function, clinical signs related to airflow limitation and serum cortisol levels in horses with experimentally induced middle to severe airway obstruction,* Equine Veterinary Journal 2019; 51; 779-786.