

## RMTC Position Statement on Clenbuterol

### Introduction

Clenbuterol is a relatively selective  $\beta_2$  adrenergic receptor agonist used for bronchodilation and increasing mucociliary clearance in the horse. In contrast to other  $\beta_2$  adrenergic receptor agonists such as albuterol and terbutaline, clenbuterol is rapidly and extensively absorbed after oral administration without extensive first-pass metabolism so that clinically effective serum or plasma concentrations are achieved.

### Chemistry

Clenbuterol (Figure 1) is 4-amino- $\alpha$ -[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol (IUPAC) typically marketed as the hydrochloride salt. Clenbuterol has one chiral center at the benzylic carbon and is administered as the racemate although most of the pharmacologic activity is attributed to the levorotatory isomer.

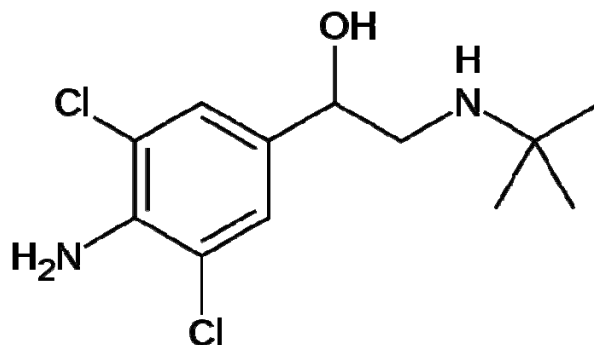


Figure 1. Chemical structure of clenbuterol.

Clenbuterol was first reported from Boehringer Ingelheim laboratories in the early 1970s and marked the end result of a search for an orally effective and longer lasting bronchodilator than had been available previously. Increased oral bioavailability was achieved by substituting halogens (chloride) for protons to the aromatic ring. A longer duration of effect and increased  $\beta_2$  adrenergic receptor selectivity was achieved primarily by substituting the tertiary butyl group for a methyl group on the secondary amine group.

Ventipulmin® is the only formulation of clenbuterol approved by the US Food and Drug Administration for use in the horse. The approved product is a viscous liquid sold by Boehringer Ingelheim Vetmedica, Inc. at a concentration of 72.5 micrograms per milliliter. No parenteral forms of clenbuterol are approved for use in any species in the US.

### Pharmacokinetics

The pharmacokinetics and disposition of clenbuterol in the horse after single and multiple dose administrations have been reported in numerous publications.<sup>i</sup> After oral administration clenbuterol is rapidly and nearly completely absorbed, reaching peak blood concentrations within a few hours of administration.<sup>ii, iii</sup>

Research regarding the pharmacokinetics of clenbuterol was recently completed at the University of California – Davis. The research indicated that it was readily absorbed when administered orally.<sup>iv</sup> At the low dose recommended by the manufacturer of 0.8 mcg/kg clenbuterol reached maximum plasma concentration in an average of 1.42 hours. Based upon a 30 day regimen of 0.8 mcg/kg twice daily, plasma levels were below detection using LC-MS at 7 days in all 22 horses sampled. Urine levels using this protocol were measurable for over 20 days.

### **Pharmacodynamics**

Clenbuterol is a selective  $\beta_2$  adrenergic receptor agonist. It works through receptors in the lungs that are coupled through G proteins to increase intracellular cyclic AMP which produces smooth muscle relaxation. The desirable actions of clenbuterol are produced by stimulation of these receptors in the airways and lungs, resulting in bronchodilation and an increase in the clearance of mucus and debris. Therefore, it is used therapeutically for the management of acute and chronic respiratory disorders in horses. It may also cause a reduction in release of allergic and inflammatory mediators from mast cells in the lungs.<sup>v</sup>

All drugs have side effects that can affect other body functions. In the horse, concentrations of clenbuterol can be found in all vital organs, including the heart and brain. Side effects can occur in the horse within 5 to 10 minutes following oral administration of clenbuterol and are due to the activation of  $\beta_2$ -adrenergic receptors in these organ systems. Moderate sweating, an increase in heart rate, nervousness, and pacing have been reported, and suggest a greater sensitivity of the horse to clenbuterol than other species in which higher doses were administered before these effects were observed.<sup>vi</sup>

### **Therapeutic Use**

In recent promotional material, the manufacturer of Ventipulmin™ specifically lists Recurrent Airway Obstruction and Inflammatory Airway Disease as diseases that clenbuterol is intended to treat. The FDA approved information provided by the manufacturer states that the indications for use of this medication are “the management of horses affected with airway obstruction, such as occurs in chronic obstructive pulmonary disease (COPD).” A copy of this material is attached to this document.

The makers of Ventipulmin™ publish the following twice daily administration regimen for clenbuterol:

- Initial dosage: administer 0.5 mL/100 lbs (0.8 mcg/kg) for 3 days (6 treatments);
- If no improvement, administer 1.0 mL/100 lbs (1.6 mcg/kg) for 3 days (6 treatments);
- If not improvement, administer 1.5 mL/100 lbs (2.4 mcg/kg) for 3 days (6 treatments);
- If no improvement administer 2.0 mL/100 lbs (3.2 mcg/kg) for 3 day (6 treatments); If no improvement, horse is non-responder to clenbuterol and treatment should be discontinued.

Based upon these dosing recommendations, the minimum length of time for effective treatment is three days with dosing twice daily and the maximum duration of treatment is twice daily for 30 days. More recently, evidence of tachyphylaxis, specifically regarding its bronchoprotective properties, was apparent by 21 days. These observations suggest that prolonged and continuous use of clenbuterol as a bronchodilator may be unjustified.<sup>vii</sup>

### **RMTC Recommendations Regarding Use of Clenbuterol**

The use of clenbuterol in performance horses has come under criticism because it is a  $\beta_2$  - adrenoreceptor agonist and because it produces a repartitioning effect. Clenbuterol is a banned

performance-enhancing substance in all sanctioned human athletic competitions. The crux of the issue is that while clenbuterol does provide for bronchodilation, clenbuterol also has repartitioning effects on skeletal muscle which mimic the anabolic effects of androgenic/anabolic steroids. WADA lists clenbuterol as a banned anabolic agent along with other  $\beta_2$  agonists.<sup>viii</sup> As discussed below, clenbuterol administration has been shown to increase muscle mass and decrease fat when used – even at therapeutic doses.

In a recent report out of New York, a task force identified clenbuterol as a major safety and integrity issue in racing. The task force reported that a significant number of horses at NYRA tracks were being administered clenbuterol – many of which were not receiving it to treat airway disease.<sup>ix</sup> Similar findings have been reported throughout the United States. Prior to the CHRB suspending authorization of clenbuterol in California, the equine medical director reported that 58% of thoroughbred horses in training and 100% of quarter horses nominated to major stakes showed detectable levels of clenbuterol in plasma samples. After much discussion, and in light of these concerns, the RMTC board voted to set the thresholds listed above with a 14 day recommended withdrawal guideline.

An important note regarding the RMTC clenbuterol recommendations is that the withdrawal guidelines only apply to the FDA approved product Ventipulmin.<sup>TM</sup> Other clenbuterol containing products are not FDA approved and have been shown to have varying amounts of clenbuterol when analyzed which can affect both the pharmacokinetics and pharmacodynamics. Second, the RMTC recommended that clenbuterol use be subject to a 140 pg/mL threshold in urine and the limit of detection in plasma or serum. The two-prong threshold was recommended to prohibit race day administration of a small amount of clenbuterol. Along with this recommendation, the RMTC provided withdrawal guidance of 14 days. These recommendations are based on scientific studies of the disposition of the lowest clinical dose of clenbuterol that can be used to treat performance horses in the United States.

This recommendation was forwarded to the Association of Racing Commissioners, International who adopted the urine and plasma thresholds recommended by RMTC. In addition, they converted the 14 day withdrawal guideline to a 14 day Restricted Administration Time (RAT).

### **Request for Further Discussion**

Recently, the United States Trotting Association (USTA) and some individuals raised the concern that the 14 day RT prevents treatment of horses that race on a weekly basis – this includes some Thoroughbreds and Quarter Horses as well as many Standardbred horses. The USTA requested that RMTC review the 14 day RT and related clenbuterol threshold recommendations as they relate to the Standardbred business model of weekly races. The USTA has requested that the RMTC consider separate medication rules for Standardbred horses that would permit clenbuterol treatment within five or fewer days of racing.

In response, the RMTC convened a discussion among experts with experience in treating and regulating the various breeds. The panel included practicing veterinarians in the Standardbred and Thoroughbred racing circuit; surgeons who treat a variety of racing breeds; and regulatory veterinarians with responsibility for regulating a variety of breeds in their jurisdictions.

More restrictive thresholds for clenbuterol are currently in place in California (21 days) and New Mexico (termed “zero tolerance”).

### **Clenbuterol Pharmacodynamic Research**

A significant amount of research has been done regarding the effects of clenbuterol on exercised horses. The vast majority of the pharmacodynamic research has been done on Standardbred horses at Rutgers University. In those studies, researchers used a 5 day on- 2 day off-treatment model at a 2.4 mcg/kg dose. Control horses and some of the horses treated with clenbuterol were exercised 3 times per week.

In one of the first studies to be published regarding repartitioning and clenbuterol, researchers measured rump fat and fat free mass in Standardbred mares.<sup>x</sup> At the first measurement – two weeks into the trial, they found a statistically significant difference in horses in the clenbuterol treatment groups regardless of exercise status. A statistically significant difference was not observed within the exercised only horses until week 4. Essentially, researchers observed a statistically significant increase in fat free mass two weeks prior in the group with clenbuterol plus exercise when compared to the group that was only exercised. Simply put – horses on clenbuterol achieve more fitness faster.

In another research paper from Rutgers, researchers examined the effect of clenbuterol on aerobic performance in horses.<sup>xi</sup> The researchers observed that treated horses experienced sweating and severe agitation beginning on day 1 of administration and continuing until day 10. In addition, researchers documented:

- a decrease in  $VO_{2max}$  in horses treated with clenbuterol and exercised and a corresponding increase in horses that were only exercised
- a decrease in time to fatigue in horses treated with clenbuterol while horses only exercised had a corresponding increase in time to fatigue
- a decrease in plasma volume in clenbuterol treated horses with a corresponding increase in exercised only horses

These changes occurred over an eight week period with intermittent clenbuterol treatment.

Researchers have also examined clenbuterol's effect on cardiac function. In yet another study from Rutgers University, researchers examined the effect of chronic low dose clenbuterol use on echocardiography results in trained Standardbred horses.<sup>xii</sup> Researchers determined that chronic clenbuterol administration caused statistically significant changes in cardiac function – particularly post exercise. Specifically, the researchers observed:

- significant stroke volume increase with accompanying increase in left ventricle internal dimension for treated horses versus non-treated horses (regardless of exercise status)
- significant increases in aortic root dimension for treated horses after 8 weeks versus untreated horses regardless of exercise status
- significant increases in left ventricular internal dimension at both systole and diastole in treated horses versus non-treated horses (regardless of exercise status)

Again, these changes were observed in eight weeks using intermittent treatment.

In 2003, researchers at Rutgers University examined histologic samples of muscle fibers taken from Standardbred horses administered clenbuterol (exercised and not exercised) and compared them to control horses (exercised and not exercised).<sup>xiii</sup> These investigators observed a decrease in type IIA muscle fibers with an increase in type IIX muscle fibers in all horses administered clenbuterol. Type IIX muscle fibers increase in horses that are in detraining. Thus, these investigators concluded that administration of clenbuterol was detrimental to exercise performance “in horses running races comparable to Standardbreds.”

Also, in a 2013 poster presented to the American College of Veterinary Internal Medicine diplomats, researchers from the University of Pennsylvania found a significant decrease in the percent of rump fat thickness after administration of clenbuterol at the low therapeutic dose of 0.8 mcg/kg for as few as 6 days.<sup>xiv</sup> In this limited study of six Standardbred horses, tracheal mucociliary clearance rate increases were not observed until day 6. In a separate study, reversal of the effects of clenbuterol on rump fat required a minimum of 11 days following completion of a 21 day administration of 0.8 mcg/kg twice daily.<sup>xv</sup>

### **Physiologic Differences Between Standardbred and Other Breeds**

The consensus of the group is that there is nothing physiologically unique about Standardbred horses that justifies different regulations. Given this and the potential risks of long term chronic administration of clenbuterol as well as the potential for abuse, the RMTC elected to consider the welfare of all horses in its threshold determination. Moreover, while a greater majority of Standardbreds race more often than other breeds, allowing a five day withdrawal time for Standardbreds (or any breed) will allow for a horse to take several weeks off of training and benefit from the anabolic effects of clenbuterol for approximately 11 days. Furthermore, in one jurisdiction, a Standardbred racing weekly could conceivably be administered clenbuterol up to 5 days a week. Absent weekly testing of out of competition horses, it would be impossible to regulate these issues.

### **Airway Disease and Thresholds**

While clenbuterol is a useful drug when used appropriately, even a short period of use within a few days of racing is a threat to integrity and the safety of the horse. As such, it is necessary to find other alternatives. In addition to clenbuterol, RMTC placed glycopyrrolate on the list of therapeutic medications. Glycopyrrolate is used to decrease bronchial secretions in the horse. It has a recommended withdrawal time of 48 hours.

In addition to glycopyrrolate, RMTC is investigating the possibility of adding nebulized albuterol (another  $\beta_2$  adrenergic receptor antagonist) and guaifenesin (an expectorant). Considerable research is published on albuterol; very little is published on the pharmacokinetics of guaifenesin.

### **Recommendations**

The recommendations of the panel are as follows:

1. Clenbuterol thresholds should remain as recommended by the RMTC and enacted by the ARCI.
2. RMTC should recommend that the ARCI remove the Restricted Administration times from the clenbuterol regulations.
3. The RMTC should work to add albuterol and guaifenesin to the list of controlled therapeutic medications as soon as possible.

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<sup>i</sup> Kallings, P., Ingvast-Larsson, C., Persson, S., Appelgren, L.E., Forster, H.J. & Rominger, K.L. Clenbuterol plasma concentrations after repeated oral administration and its effects on cardio-respiratory and blood lactate responses to exercise in healthy Standardbred horses. *Journal of Veterinary Pharmacology and Therapeutics* **14**, 243– 249 (1991); Harkins, J.D., et al, *Clenbuterol in the horse: urinary concentrations determined by ELISA and GC/MS after clinical doses*, *J. vet. Pharmacol. Therap.*, **24**: 7-14 (2001); Knych, H.K., et al, *Detection, pharmacokinetics and cardiac effects following administration of Clenbuterol to exercised horses*, *Equine Vet J.* 2013 Jun 17. doi: 10.1111/evj.12118. [Epub ahead of print]

<sup>ii</sup> Soma L.R., Uboh C.E., Guan, Moate, F.P., Luo, Y., Teles, D., Li, R, Birks, E.K., Rudy, J.A., & Tsang, D.S.. Pharmacokinetics and disposition of clenbuterol in the horse. *Journal of Veterinary Pharmacology and Therapeutics* **27**: 71-77 (2004).

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- <sup>vi</sup> [Read JR](#), [Boston RC](#), [Abraham G](#), [Bauquier SH](#), [Soma LR](#), [Nolen-Walston RD](#)., Effect of prolonged administration of clenbuterol on airway reactivity and sweating in horses with inflammatory airway disease. *Am J Vet Res.* 2012 Jan;**73**(1):140-145.
- <sup>vii</sup> [Read JR](#), [Boston RC](#), [Abraham G](#), [Bauquier SH](#), [Soma LR](#), [Nolen-Walston RD](#)., Effect of prolonged administration of clenbuterol on airway reactivity and sweating in horses with inflammatory airway disease. *Am J Vet Res.* 2012 Jan;**73**(1):140-145.
- <sup>viii</sup> Available at: [http://www.wada-ama.org/Documents/World\\_Anti-Doping\\_Program/WADP-Prohibited-list/2013/WADA-Prohibited-List-2013-EN.pdf](http://www.wada-ama.org/Documents/World_Anti-Doping_Program/WADP-Prohibited-list/2013/WADA-Prohibited-List-2013-EN.pdf)
- <sup>ix</sup> New York Task Force on Racehorse Health and Safety, *Investigation of Equine Fatalities at Aqueduct 2011-2012 Fall/Winter Meet* (2012).
- <sup>x</sup> Kearns, C.F., *et al*, *Chronic administration of therapeutic levels of clenbuterol acts as a repartitioning agent*, *J. Appl Physiol*, **91**:2064-70 (2001).
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- <sup>xii</sup> Sleeper, M.M., Kearns, C.F., and McKeever, K.H., *Chronic clenbuterol administration negatively alters cardiac function*, *Medicine and Science in Sports and Exercise*, (2002).
- <sup>xiii</sup> Beekley, M.D., *et al*, *Chronic clenbuterol administration alters myosin heavy chain composition in standardbred mares*, *The Veterinary Journal*, **165**:234-39 (2003).
- <sup>xiv</sup> Barr, C.A., *et al*, *The effect of chronic clenbuterol administration on mucociliary clearance and body fat in adult horses*, *ACVIM Poster* (2013).
- <sup>xv</sup> Personal communication by Dr. Mary Robinson with Dr. Rose Nolen-Walston.