Docket No. FDA-2018-N-4626 for "Lists of Bulk Drug Substances for Compounding: Office Stock Drugs for Use in Nonfood-Producing Animals or Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species."
Nominator: Wedgewood Pharmacy
Nominator contact info: Meghann Abbott, mabbott@wedgewoodpharmacy.com
Date submitted to FDA: 12/5/2023
Nomination description: Guanabenz Acetate
Supporting documentation attached: Sources cited

Instructions: Each bulk drug substance should be submitted to the docket as its own, separate nomination. Submissions to the docket containing more than one bulk drug substance will not be considered an adequate nomination and will not be reviewed. Nominated substances that do not meet the definition of a bulk drug substance will not be evaluated for inclusion on a List.	
1. Description of the Bulk Drug Substance:	
(a) Chemical name(s); (b) common name(s);	(A.) Hydrazinecarboximidamide, 2-[(2,6-dichlorophenyl)methylene], monoacetate; [(2,6-Dichlorobenzylidene)amino]guanidine monoacetate (B.) Guanabenz Acetate
2. Description of the Animal Drugs That Will be Compounded with the Nominated Bulk Drug Substance:	
(a) Dosage form(s) into which the bulk drug substance will be compounded (*e.g.,* capsule, tablet, suspension);	(B.) Injection Solution Oral Suspension Oral Paste
(b) strength(s) of the compounded drug(s); and	(B.) Injection Solution – 2mg/ml Oral Suspension – 2mg - 20mg/ml Oral Paste – 2mg – 10mg/ml Note: In accordance with FDCA Section 503A regulations this nomination is understood not to include anything that is within +/- 10% of the strength of any commercially available FDA approved drug product in the same dosage form as listed in section 3 (c).
(c) intended route(s) of administration of the compounded drug(s) (*e.g.,* oral, topical, injection, etc.).	(C.) Injection Solution – Intravenous, Intramuscular Oral Oil Suspension – Oral Oral Paste – Oral
3. Information Requested for FDA to Evaluate Bulk Drug Substances for Inclusion on a List:	

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(a) The species the drug to be compounded with the nominated bulk drug substance is intended to treat;	(A.) Injection Solution - Equine Oral Oil Suspension - Equine Oral Paste- Equine
(b) The disease or condition(s) the drug to be compounded with the nominated bulk drug substance is intended to treat;	(B.) Anti-hypertensive Agents Alpha-2 Adrenergic Agonists Sedation and Analgesia (Source: Harkins, J.D. and Tobin, T. (2003) Pharmacodynamics of Guanabenz and related a2 agonist. In. *Proceedings of the 14th International Conference of Racing Analysts and Veterinarians*. Eds: D.W. Hill and W.T. Hill. R and W Publications Ltd., Newmarket. p 34.)
(c) If there is a marketed FDA-approved, conditionally approved, or indexed animal drug(s) that addresses the same condition(s) in the same species, an explanation of why a compounded drug is necessary (*e.g.*, why FDA-approved, conditionally approved, or indexed animal drug(s) is not suitable for a particular animal population);	(C.) Veterinary Manufactured: There are no FDA approved veterinary manufactured products containing Guanabenz Acetate available. In a 2022 comparative study, it was concluded that Guanabenz not only provided a more intense, longer-lasting sedation than its counterparts but also delivered a quicker response time to reach sedative effect. Additionally, only Guanabenz was found to produce an antinociceptive response, which is the body's response to potentially harmful provocation. (Lehner, Andreas F., et al. "Guanabenz in the Horse-A Preliminary Report on Clinical Effects and Comparison to Clonidine and Other Alpha-2 Adrenergic Agonists." Veterinary Science, Toxicology and Cancer Biology. 2022. 38 (6). 554–65.) A study performed in 2006 on the effects of adrenergic suppression in Thoroughbred racehorses found cortisol levels to be decreased after being administered with Guanabenz. As a result of

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	the reduction in cortisol, horses were less responsive to physiological stimuli allowing for an increase in focus. (Colahan, P. T., et al. "The Effect of Adrenergic Suppression Induced by Guanabenz Administration on Exercising Thoroughbred Horses." *Equine Veterinary Journal*. 2006. 38(36) 262–66) In veterinary medical applications, it was recorded that equine veterinarians were injecting Guanabenz prior to racing due to its ability to lower the horses blood pressure, thereby reducing the incidence and/or severity of Exercise-induced pulmonary hemorrhage (EIPH). (Tobin, Thomas, "Long Acting, Reversible Veterinary Sedative and Analgesic and Method of Use" (2006). Veterinary Science Faculty Patents. 14.)
(d) Confirmation that there is no marketed FDA-approved, conditionally approved, or indexed drug(s) that could be prescribed to treat the condition in the species that the drug compounded with the nominated substance is intended to address;	(D.) Human Manufactured: There are no FDA approved veterinary or human manufactured products containing Guanabenz Acetate available. Depending upon indication for treatment there may be other drugs in the same therapeutic class as Guanabenz Acetate that are FDA approved for human use available, but Guanabenz Acetate is deemed necessary by veterinarians over other options in certain patients due to superior efficacy, concerns over side effects or interactions from alternate agents, lack of availability of appropriate dose/dosage forms for alternate agents, or individual patient needs. Dormosedan® (Detomidine) is a relatively short acting sedative with a slow onset. Maximum sedation and analgesia were achieved in approx. 15 minutes with a duration of up to 1 hour when given intravenously. It can also cause unprovoked aggression and ataxia. Detomidine can be used alone or in combination with opioids for chemical restraint for a variety of standing procedures. When administered a single dose of Detomidine, horses displayed signs

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	of bradycardia for less than 1 hour compared to approximately 3.5 hours in those injected with Guanabenz. Rompun® (Xylazine) produces maximum calming effects, sedation, muscle relaxation and analgesia within 10 minutes of IV injection, with most effects subsiding after a mere 30 minutes. In horses that are already excited, agitated or in pain, clinically acceptable doses may not yield adequate sedation thus Guanabenz would be the preferred option. (Hubbell, J., Practical Standing Chemical Restraint of the Horse. AAEP Proceedings. 2009. 55. 2-6.) (Cole, Cynthia, et. al. "Anesthesia and sedation in the field." *Equine Pharmacology*. 1st ed., 2015.)
(e) If known by the nominator, if the bulk drug substance is an active ingredient in a marketed FDA-approved, conditionally approved, or indexed animal or human drug(s), an explanation of why the animal drug cannot be compounded from the marketed FDA-approved, conditionally approved, or indexed animal or human drug(s).	(E.) N/A
(f) If known by the nominator, a description of any human user or animal safety concerns associated with use of the nominated bulk drug substance or finished compounded drug for the condition(s) in the species that the compounded drug is intended to address. If there are concerns, an explanation of why the concerns should not	(F.) Guanabenz Acetate has been deemed safe and effective in equines. Common adverse reactions found when using α2-agonists are sunken eyelids, lowering of the head and sagging of the lower lip. (Lehner, Andreas F., et al. "Guanabenz in the Horse-A Preliminary Report on Clinical Effects and Comparison to Clonidine and Other Alpha-2 Adrenergic Agonists." Veterinary Science, Toxicology and Cancer Biology. 2022. 38 (6). 554–65.)

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preclude inclusion of that bulk drug substance on the List;	Per Wytensins'™, drug insert, most symptoms associated with therapy involved the nervous system such as drowsiness, dizziness, weakness, and dry mouth. Compounded Guanabenz Acetate formulations as proposed in section #2(a) pose no risk to human caregivers beyond that of the previously commercially manufactured FDA approved Guanabenz Acetate (Wytensin™) preparation. ("Wytensin Side Effects: Common, Severe, Long Term." *Drugs.Com*, https://www.drugs.com/sfx/wytensin-side-effects.html. Accessed 3 Nov. 2023.)
(g) For compounded drugs intended as office stock for nonfood-producing animals, an explanation of why the animal drug to be compounded with the nominated bulk drug substance is important to be available to the veterinarian for urgent treatment to avoid animal suffering or death, *e.g.*, why animal suffering or death will result if treatment is delayed until a compounded animal drug can be obtained pursuant to a prescription for an individually identified animal; and	(G.) Veterinarians administer Guanabenz Acetate in urgent and routine situations. Office stock of compounded Guanabenz Acetate is imperative so veterinarians may initiate the necessary surgical and routine treatments needed. Alpha2-adrenoceptor agonists are used to provide sedation, analgesia, and muscle relaxation. However, due to their diverse pharmacological effects, each is used in distinct procedures. Exercise-induced pulmonary hemorrhage (EIPH) occurs in approximately 75% of all racehorses. It is defined as a respiratory condition in which the capillaries within the lungs rupture causing the red blood cells to spill into the airways following strenuous exercise. Since many equines never display obvious outwards signs of EIPH, many episodes may occur prior to diagnosis, resulting in chronic and cumulative damage to the lungs. (Reed, Stephen, and Elizabeth Davis. Disorders of the Respiratory System. *Equine Internal Medicine*. 4th ed. 2018. (313-386).) Guanabenz Acetate is necessary for office stock because it allows veterinarians access to a prompt analgesia/sedation for minor emergent or routine standing procedures. Guanabenz Acetate's rapid onset, long duration of action and antinociceptive activity allows for it to be a safer alternative when practicing in the field.

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(h) For compounded drugs intended for use as antidotes to treat toxicoses in food-producing animals, or as sedatives or anesthetics for free-ranging wildlife species, relevant scientific literature or other evidence that demonstrates that the prescribing veterinarian has a basis for determining appropriate withdrawal, withholding, or discard time(s) for meat, milk, eggs, or any food which might be derived from the treated animal(s).		