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FREEDOM OF INFORMATION SUMMARY
ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-533

Aservo[®] EquiHaler[®]

Ciclesonide inhalation spray

Horses

Aservo[®] EquiHaler[®] is indicated for the management of clinical signs associated with severe equine asthma in horses.

Sponsored by:

Boehringer Ingelheim Animal Health USA, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-533

B. Sponsor

Boehringer Ingelheim Animal Health USA, Inc.
3239 Satellite Blvd.
Duluth, GA 30096

Drug Labeler Code: 000010

C. Proprietary Name

Aservo[®] EquiHaler[®]

D. Drug Product Established Name

Ciclesonide inhalation spray

E. Pharmacological Category

Glucocorticoid

F. Dosage Form

Aservo[®] EquiHaler[®] is a non-pressurized metered dose inhaler and drug cartridge combination. The drug cartridge contains an inhalation solution which is dispensed by the inhaler into the horse's left nostril as a spray.

G. Amount of Active Ingredient

343 mcg ciclesonide/actuation

H. How Supplied

Each inhaler contains sufficient drug to provide 140 actuations (puffs) to the horse.

I. Dispensing Status

Rx

J. Dosage Regimen

The initial dose of Aserveo[®] EquiHaler[®] is 8 actuations (2744 mcg ciclesonide) twice daily for 5 days, followed by 12 actuations (4116 mcg ciclesonide) once daily for 5 days.

K. Route of Administration

Intranasal inhalation

L. Species/Class

Horses

M. Indication

Aservo® EquiHaler® is indicated for the management of clinical signs associated with severe equine asthma in horses.

II. EFFECTIVENESS

The disease now known as "severe equine asthma" has been subject to several changes in the name over the years. At various times in the past, the disease was known as heaves, chronic pulmonary obstructive disease (COPD), and during initial development of Aservo® EquiHaler®, recurrent airway obstruction (RAO). A variation of RAO, known to specifically be associated with outdoor antigens, was known as summer pasture associated obstructive pulmonary disease (SPAOPD). RAO and SPAOPD share many clinical features except for the inciting antigens, and are both considered to be included in the name "severe equine asthma." Management of severe equine asthma should consider all contributing factors of the disease, including environmental changes which aim to reduce exposure to the underlying antigenic trigger where possible. The pathophysiologic components of the disease include inflammation and bronchoconstriction. Aservo® EquiHaler® is therefore considered part of the overall management of severe equine asthma. Glucocorticoids would not be expected to resolve bronchoconstriction, and therefore administration of bronchodilators may also be appropriate.

A multi-site field study was conducted to evaluate the effectiveness and safety of Aservo® EquiHaler® in horses with severe equine asthma. The field study was designed with two distinct phases. Phase 1 was designed to assess the effectiveness of Aservo® EquiHaler®, compared to a vehicle control product, while minimizing other possible influences on the horse's clinical signs (including other interventions). Phase 2 was designed to evaluate the safety of repeated use of Aservo® EquiHaler® if needed for continued control of the clinical signs associated with severe equine asthma, while also allowing concomitant use of additional environmental and pharmaceutical interventions. Phase 2 collected field use and safety information for the duration of an expected season; most horses would be expected to have the worst clinical signs during specific times of year, or "season" when the environmental antigens levels are increased. Both Phases evaluated the ease of use and acceptance by the horse of the inhaler device.

A. Dosage Characterization:

The dosing schedule of 8 actuations (2744 mcg ciclesonide) twice a day for five days, followed by 12 actuations (4116 mcg ciclesonide) once a day for five days, (for a total of ten days of treatment) was selected based on three dose finding studies conducted in horses with experimentally induced airway obstruction (study 2011040, 2012053, and 2013074) and two pilot clinical field studies (study 2013184 and 2014108). A non-clinical bridging study (BI Study Number 4_6) was also performed to compare the performance of the pilot drug delivery device used in study 2013184 with the final drug delivery device used in study 2014108. These studies are summarized below.

1. Dose Finding Studies:

In the dose finding studies, horses were exposed to moldy hay to induce airway obstruction. Each study utilized 8 horses with RAO in a blinded randomized crossover study design. Ciclesonide was administered by inhalation to adult horses at different dose levels ranging from 450 mcg up to 3712.5 mcg, once or twice daily, using a pilot dosing device (non-pressurized metered dose inhaler). The studies compared treatment with the various doses of ciclesonide to negative control (administration of the pilot dosing device without ciclesonide) and dexamethasone administered orally (0.066 mg/kg) for 14 days. The effect of ciclesonide was assessed by evaluating lung function variables (transpulmonary pressure (Δ PL), lung resistance (RL), and lung elasticity (EL)) and clinical assessments (including evaluation of breathing effort). Safety assessments included evaluation for lameness and clinical pathology. Treatment with 2700 mcg ciclesonide twice daily resulted in significant improvement, after 7 and 14 days administration, of both the lung function variables and weighted clinical score when compared to pre-treatment values. This effect was comparable to dexamethasone administered orally and significantly better than negative control.

2. Pilot Clinical Field Studies:

Two pilot prospective, randomized, double-blinded, multicenter, field studies were conducted in the European Union. Enrolled client owned horses were diagnosed with RAO and/or SPAOPD prior to treatment. Effectiveness was evaluated by assessing for clinical improvement in treated horses using a modified clinical score adapted from Tesarowski et al., 1996,¹ assessed pre and post-treatment.

In study 2013184, a pilot drug delivery device was used to administer a target dose of 2700 mcg ciclesonide twice daily for five days followed by the administration of 4050 mcg once daily for an additional five days. A total of 73 client owned adult horses previously diagnosed with RAO and/or SPAOPD were enrolled and treated with either ciclesonide (N=43) or placebo control (N=30); 70 horses were evaluated for effectiveness and 73 horses were evaluated for field safety. Ciclesonide treated horses showed greater clinical improvement (reductions in weighted clinical scores) between Day 1 and Day 5 or 10 versus horses treated with placebo control.

In study 2014108, the final drug delivery device was used to administer 2744 mcg ciclesonide twice daily for five days followed by the administration of 4116 mcg once daily for an additional five days. A total of 223 horses previously diagnosed with RAO and/or SPAOPD were enrolled and treated with either ciclesonide (N=110) or placebo control (N=113); 220 horses were evaluated for effectiveness and 224 horses were evaluated for field safety. Horses treated with ciclesonide showed improvement in clinical signs of RAO and/or SPAOPD when compared to placebo control.

¹ Tesarowski D.B., Viel L., McDonnell W. (1996) Pulmonary function measurements during repeated environmental challenge of horses with recurrent airway obstruction. AJVR, Vol 57, No.8

3. Non-Clinical Bridging Study:

A bridging study (BI Study Number 4_6) was conducted to compare the performance of the pilot drug delivery device used in study 2013184 with the final drug delivery device used in study 2014108. Testing of multiple actuations of 10 inhalers for both devices revealed <5% difference in average dose delivery between the devices.

B. Substantial Evidence

Field Effectiveness Study

Title: Efficacy and Safety Field Study of Ciclesonide for Horses with Recurrent Airway Obstruction (RAO) and/or Summer Pasture Associated Obstructive Pulmonary Disease (SPAOPD). (Study No. 2014368)

Study Dates: June 2016 to October 2019

Study Locations: 26 veterinary clinics in the United States participated in this multi-center field study, in the following locations:

Pell City, Alabama	Browns Summit, North Carolina
Exeter, California	Rhinebeck, New York
Brandon, Florida	Scottsville, New York
Clermont, Florida	Apollo, Pennsylvania
Tallahassee, Florida	Glen Rock, Pennsylvania
Canton, Georgia	Quakertown, Pennsylvania
Spencer, Indiana	Aiken, South Carolina
Baton Rouge, Louisiana	Amarillo, Texas
Ann Arbor, Michigan	Montgomery, Texas
Ortonville, Michigan	Earlsville, Virginia
Canton, Missouri	Ridgefield, Washington
Peculiar, Missouri	Lodi, Wisconsin
Three Forks, Montana	Ranson, West Virginia

Study Design:

Objective: In Phase 1, the objective was to evaluate the effectiveness and safety of Aservo® EquiHaler® compared to the control product (CP) for 10 days in horses with severe equine asthma. In Phase 2, repeated use and field safety information were obtained for an additional 90 days, during which time enrolled horses could be treated with Aservo® EquiHaler® as needed for recurrence of clinical signs. The study was conducted in accordance with good clinical practice (GCP) guidelines.

Study Animals: The study enrolled 320 client- and university-owned horses with severe equine asthma (137 female, 183 male) of various breeds. Enrolled horses were 6-34 years old. Horses were identified as having RAO (61%), SPAOPD (30%), or both (9%). To be eligible for enrollment, horses were required to have

a Weighted Clinical Score (WCS) ≥ 11 (see description of WCS under Measurements and Observations below), and a body weight of at least 200 kg. In order to ensure that horses had severe asthma, the inclusion criteria required a diagnosis of RAO and/or SPAOPD with observation of at least one clinical sign for 14 days or more prior to enrollment, a history of at least two previous episodes of labored breathing at rest, and a history of improvement with appropriate treatment (for example, glucocorticoid administration, bronchodilator administration, and/or change in environment).

Horses were excluded from the study if they were intended for breeding, were pregnant or lactating, were suspected to have acute infectious lower airway disease, had known upper respiratory tract disorders, had abnormalities of the left nostril or a small nostril size preventing proper administration of test article, or displayed a temperament which would prevent proper administration of test article. Horses with elevated white blood cell counts at baseline were removed from further participation from the study, even if they otherwise met the inclusion criteria. Prior to enrollment, horses were not allowed to have been treated for their current asthma episode, including a change in environment or feed, for the previous 14 days.

Experimental Design: Multi-center, vehicle-controlled, randomized, masked field study (Phase 1) and repeated use field safety study (Phase 2). At the start of Phase 1, horses were enrolled and randomized in a 1:1 ratio to receive either Aservo[®] EquiHaler[®] or the control product (CP). Masking was maintained by assigning unique identification numbers, provided by the Electronic Data Capture (EDC) system, to all Aservo[®] EquiHaler[®] and control product inhalers upon confirmation of enrollment. Neither site personnel nor owners were aware of treatment assignments in Phase 1.

For Phase 2, 108 horses were allowed to enroll following completion of Phase 1. Horses were monitored by the owners and received regular or unscheduled examinations as needed by the Investigators. If on re-examination horses had a $WCS \geq 9$, horses were administered a 10-day course of treatment with Aservo[®] EquiHaler[®] regardless of original treatment group assignment. Following the 10 days of Aservo[®] EquiHaler[®], the horses were re-examined by the Investigator. It was possible for horses to receive continuous repeated 10-day courses of treatment with Aservo[®] EquiHaler[®] for the whole 100-day period if needed based on WCS. Environmental changes and additional therapies to manage the clinical signs of asthma were allowed during Phase 2. Phase 2 enrollment was limited to the first 108 horses that were eligible, and therefore not all Phase 1 horses continued into Phase 2.

Drug Administration: Ciclesonide inhalation spray (as Aservo[®] EquiHaler[®]) or control product was administered by intranasal inhalation via the EquiHaler[®] placed in the left nostril of the horse. In Phase 1, horses received either Aservo[®]

EquiHaler[®], the investigational veterinary product containing the active ingredient ciclesonide, or the control product, consisting of an identical inhaler device containing the vehicle with no ciclesonide (see Table II.1 below). In Phase 2, all horses received Aservo[®] EquiHaler[®] as needed (see Experimental Design above) with the same 10-day course of treatment as in Phase 1.

Table. II.1. Phase 1 Treatment Groups

Group	Dosage	Number of Horses
Aservo [®] EquiHaler [®]	Days 1-5: 8 actuations (puffs) twice daily (5488 mcg ciclesonide per day) Days 6-10: 12 actuations (puffs) once daily (4116 mcg ciclesonide per day)	163 ^a
Control Product (CP)	Days 1-5: 8 actuations twice daily (0 mcg ciclesonide per day) Days 6-10: 12 actuations once daily (0 mcg ciclesonide per day)	156

^aOne horse was enrolled but did not receive any treatment.

Measurements and Observations: For Phase 1, baseline physical examination and calculation of WCS (adapted from Tesarowski et. al.², see Table II.2 below) were performed and blood samples for hematology, biochemistry, and fibrinogen were obtained prior to the initial dose administration and again at Day 10. Dose administration was initiated on Day 1, and effectiveness was evaluated on Day 10. The Investigator telephoned horse owners on Day 5 to assess any abnormal observations.

The WCS was the primary effectiveness variable for Phase 1. Horses were considered a treatment success if they showed a reduction in their WCS by at least 30% between Day 0/1 and Day 10 and had a Day 10 WCS \leq 14. Table II.2 describes the score assigned to each of the following parameters: respiratory rate, nasal discharge, nasal flaring, abdominal lift, tracheal sounds, bronchial tones, crackles, wheezes and cough. For each parameter, the Investigator selected a single score that fit the horse's clinical signs at the time of the examination, and these were summed to result in the final WCS for that study day.

² Tesarowski DB, Viel L, McDonell WN. Pulmonary function measurements during repeated environmental challenge of horses with recurrent airway obstruction (heaves). 1996; *Am J of Vet Res.* 57(8): 1214-1219.

Table II.2. Weighted Clinical Score

Parameter	Score: Description
Respiratory rate (breaths/minute)	0: <16 bpm 1: 16-20 bpm 2: 21-25 bpm 3: 26-30 bpm 4: >30 bpm
Nasal Discharge	0: None 1: Serous 2: Mucous 3: Mucopurulent
Nasal Flaring	0: None 1: Present
Abdominal Lift	0: None 1: Mild movement of abdomen and/or thorax and/or anus (with or without perceptible heaves line) 3: Pronounced movement of abdomen and/or thorax and/or anus (with or without perceptible heaves line)
Tracheal Sounds	0: Normal 1: Increase in intensity 3: Mucus Movement
Bronchial Tones	0: Normal 2: Audible ventral and/or dorsal sounds
Crackles	0: None 2: Present
Wheezes	0: None 2: Present
Cough	0: None 1: Inducible by moderate pressure signal on larynx (only to be checked in the absence of intermittent or paroxysmal cough) 2: Intermittent 3: Paroxysmal

Phase 2 consisted of the first 108 horses (with owner consent) to complete Phase 1 of the study. Phase 2 began on Day 11 and continued for the following 90 days. During this phase, horses were monitored for recurrence of clinical signs to determine the need for repeat administration of Aservo® EquiHaler®. In Phase 2, regular visits by the Investigator were scheduled for Days 20, 30, 40, and 60. However, owners monitored their horses at home, and unscheduled visits could occur based on worsening clinical signs. Blood samples for hematology, biochemistry and fibrinogen were obtained at Study Day 40 and at Study Exit (Day 100). In addition, at Study Exit (Day 100) a final physical examination was conducted.

Statistical Methods: Treatment success was analyzed using a Generalized Linear Mixed Model. The model included random effects of site and site by treatment group and a fixed effect representing treatment group. A hypothesis

test comparing group means was conducted as a contrast of the Least-Squares means using a Type III F-test. Hypothesis testing was 2-sided, using a 0.05 level of significance.

Results: Of the 320 enrolled horses, 258 horses were included in the effectiveness analysis. A summary of treatment success at Day 10 is presented in Table II.3.

Table II.3. Summary of Treatment Success

Treatment Received	Number of Horses	Success Rate	P-value*
Aservo [®] EquiHaler [®]	134	52%	0.0187
Control Product	124	33%	

*P-value <0.05 indicates a significant difference at two-sided $\alpha=0.05$.

When recording dose administration, the Owners rated the horse's acceptance of the device as excellent, good, or poor on each day. On Day 1, acceptance of the device was rated as poor in 14.4% of horses in the Aservo[®] EquiHaler[®] group and 21.4% of horses in the control group on Day 1. On Day 10, acceptance was rated as poor in 7.2% of horses in the Aservo[®] EquiHaler[®] group and 7.4% of horses in the control group. Horses that were enrolled but did not receive full dosing, or were removed during Phase 1 due to poor acceptance of the device, were included in the analysis as treatment failures (7 ciclesonide and 5 control horses).

Eighty-eight of 108 horses participating in Phase 2 completed Phase 2. The most common reason horses were withdrawn early from Phase 2 was for perceived lack of effectiveness. During Phase 2, horses were prescribed a 10-day course of the Aservo[®] EquiHaler[®] when the WCS was ≥ 9 . Horses could be retreated with a full 10-day course of Aservo[®] EquiHaler[®] a maximum of nine times. Eight horses did not have a WCS ≥ 9 during Phase 2 and did not receive any courses of Aservo[®] EquiHaler[®]. Of the 100 horses who qualified for retreatment, 52 (52%) received one to three additional 10-day courses of Aservo[®] EquiHaler[®]. Twenty-three horses received seven to nine repeated courses of treatment during Phase 2. Two horses originally assigned to the Aservo[®] EquiHaler[®] group received nine full repeated courses of treatment in Phase 2, resulting in 100 days of exposure to ciclesonide.

During Phase 2, the most commonly prescribed concomitant medications for the overall management of the clinical signs of severe equine asthma included bronchodilators (n=13) and antihistamines (n=6). Systemic antimicrobials were prescribed in six horses where the primary disease did not seem adequately controlled, clinical signs worsened despite continued administration of Aservo[®] EquiHaler[®], or clinical signs of infection developed. Two horses received

dexamethasone because their disease was insufficiently controlled, and both horses exited Phase 2 early for perceived lack of effectiveness.

The most common environmental changes implemented during Phase 2 included soaking or steaming the hay, changing the forage source to either hay cubes or silage, changing the hay source (including stopping access to round bales), and increasing time out on pasture.

Adverse Reactions: Adverse reactions that were reported in Phase 1 are listed in Table II.4. The most common adverse reaction reported was coughing either during or immediately following inhalation of the test article (both Aservo[®] EquiHaler[®] and control groups). All horses that received at least one dose of test article were included in the summary of adverse reactions.

Table II.4. Number of Horses* (%) with Adverse Reactions, Phase 1

Adverse Reaction	Aservo[®] EquiHaler[®] (N=163) n (%)	Control Product (N=156) n (%)
Cough	27 (16.6)	27 (17.3)
Nasal Discharge	17 (10.4)	17 (10.9)
Leukocytosis and/or neutrophilia	10 (6.1)	7 (4.5)
Sneezing	5 (3.1)	3 (1.9)
Nasal irritation/bleeding	2 (1.2)	3 (1.9)
Increase in serum Sorbitol Dehydrogenase (SDH)	3 (1.8)	0 (0)
Hives	1 (0.6)	0 (0)

*Horses may have had one or more reports of a given adverse reaction

Because cough is also a common clinical sign of severe equine asthma, reports of cough were assessed to determine the likelihood of relation to dose administration. Most of the cases considered adverse reactions were reported to occur either during or immediately following dosing with the inhaler, or the cough was reported to worsen following use of the inhaler. The numbers of horses exhibiting coughing were similar between treatment groups, suggesting the cough was related to route of administration rather than the ciclesonide in the Aservo[®] EquiHaler[®]-treated horses. Similarly, nasal discharge, despite being a clinical sign associated with severe equine asthma, was considered possibly related to treatment with either ciclesonide or vehicle because the inhaler is inserted in the nostril.

Leukocytosis and/or neutrophilia developed in Phase 1 in several horses in both treatment groups, and in eight horses in Phase 2. Leukocytosis and/or neutrophilia was considered a possible adverse reaction, as corticosteroids can

have this effect, also known as a stress leukogram. Some horses also had concurrent clinical signs of infection, such as fever, which may have contributed to leukocytosis. One Aservo® EquiHaler®-treated horse developed fever and leukocytosis characterized by a mature neutrophilia on Day 10 that was not present at screening. Other horses had possible alternate explanations for a stress leukogram, such as pain from a hoof abscess or poor acceptance of the device which may have caused stress from the study procedures. Most Aservo® EquiHaler®-treated horses that developed leukocytosis were treatment failures on Day 10, due to failure to improve the WCS by 30%; however, three horses in the ciclesonide group and one horse in the control group were treatment successes.

In Phase 1, five horses in both treatment groups were reported to have nasal soreness, bleeding, scabs in the nostril, and redness of the nostril. In Phase 2, horses were reported to have epistaxis (2 horses), blood tinged discharge (1 horse), nose bloody and raw (1 horse), sensitive nostril (1 horse), and bright pink color of nasal mucus membranes (1 horse). One case of epistaxis was reported nine days after the last dose administered, and one case was reported from the right nostril less than 24 hours following the last dose. The one case of blood tinged discharge from the left nostril was reported 11 days following the last dose administered. These cases were considered possibly related to treatment due to the route of administration (intra-nasal).

In Phase 1, there were three ciclesonide-treated horses that had increases in serum sorbitol dehydrogenase (SDH) above the reference range on Day 10 (high values were 12.4, 18.1, and 30.4 U/L; reference range 2-6 U/L). None of these horses had clinical signs associated with this increase. One horse also had an increase in serum gamma-glutamyltransferase (GGT) above the reference range, but the GGT value at baseline was already above the reference range. By Day 40 of Phase 2, and again when measured at Day 100, this horse's SDH and GGT values were within normal limits. In Phase 2, one horse developed an elevation in SDH (63.8 U/L) following the 6th course of treatment with Aservo® EquiHaler®. This horse had elevations in alkaline phosphatase (269 U/L; reference range 76-262 U/L), aspartate aminotransferase (511 U/L; reference range 194-431 U/L), and GGT (128 U/L; reference range 9-37 U/L). Reported adverse events in this horse at various time points during the study included coughing, nasal discharge, tachycardia, and hyperthermia. The owner opted to withdraw the horse from the study after the abnormal clinical pathology results were reported (approximately Day 75).

In Phase 1, one horse developed severe hives approximately 30 minutes after administration of ciclesonide on Day 2 (following the 4th administration). The horse was withdrawn from the study due to this adverse reaction.

Adverse reactions reported in Phase 2 are listed in Table II.5. The reported reactions similar to those reported in Phase 1, with the exception of three horses that exhibited laminitis during Phase 2.

Table II.5. Number of Horses* (%) Adverse Reactions, Phase 2

Adverse Reaction	Aservo® EquiHaler® (N=100) n (%)
Cough	12 (12%)
Nasal Discharge	13 (13%)
Leukocytosis and/or neutrophilia	8 (8%)
Nasal irritation/bleeding	6 (6%)
Laminitis	3 (3%)
Sneezing	2 (2%)
Increase in serum Sorbitol Dehydrogenase (SDH)	1 (1%)

*Horses may have had one or more reports of a given adverse reaction

Three horses were reported with laminitis in Phase 2. Two of the horses with laminitis had history of previous laminitic episodes. One of these horses in the Aservo® EquiHaler® group, developed an exacerbation of laminitis on Day 14, following initial administration of ciclesonide in Phase 1. The veterinarian continued to prescribe Aservo® EquiHaler® throughout Phase 2 as directed by the protocol (for 2 additional rounds of treatment), but the drug product was ultimately discontinued due to remission of the clinical signs of asthma. The horse completed the study and intermittent clinical signs of chronic laminitis persisted until the end of the study. The other horse was administered the control product during Phase 1. Laminitis was reported three days following the third of three cycles of ciclesonide administration. Clinical signs persisted to the end of the study.

The horse with no prior history of laminitis was initially treated for thrush, and responded to conservative therapy within a few weeks. No definitive diagnosis of laminitis was made, and the examining veterinarian concluded the horse's environment played a role in the development of clinical signs.

Conclusions: Study 2014368 demonstrates the Aservo® EquiHaler® is effective for the management of the clinical signs associated with severe equine asthma. Adverse reactions associated with the administration of Aservo® EquiHaler® included coughing, nasal discharge, leukocytosis, sneezing, nostril irritation/nasal bleeding, laminitis, and increased serum SDH.

III. TARGET ANIMAL SAFETY

Target Animal Safety (TAS) is supported by a laboratory TAS study and a pharmacokinetic study. The dosing regimen is the same for all adult horses, regardless of body weight. The only size-limiting factor is whether the nasal adaptor portion of the device fits into a horse's nostril for proper administration. Therefore, because the dosing instructions on the label include the same dose regardless of horse body weight, light-weight horses were specifically included in the safety study to assess the safety of the highest mg ciclesonide/kg body weight dose when the product is administered according to the label.

The pharmacokinetic study compared the drug exposure in average and light-weight horses. Horses that weighed up to 380 kg were determined as "light-weight". The pharmacokinetic study data showed that there was higher and more variable drug exposure in the light-weight horses compared to the average weight horses. Therefore, to assess safety in light-weight horses, the TAS included two light-weight horses per treatment group.

The TAS study evaluated dosing at 1X, 2X, and 3X the label dose, compared to control product. The multiples of dose were selected based on the logistics of administering the test article at higher multiples of dose by the nasal inhalation route of administration. For this TAS study, horses that weighed less than 300 kg were determined to be "light-weight". Two light-weight horses in the highest dose ciclesonide-treatment group (3X) had evidence of cortisol suppression, with no associated clinical abnormalities. Additionally, one light-weight horse in the 2X group and two light-weight horses in the 3X group had minor elevations in serum SDH. None of these serum parameters were associated with clinical abnormalities. Therefore, the lack of clinical findings in the TAS study supports the overall safety of Aservo® EquiHaler® in light-weight and average weight horses.

A. Target Animal Safety Study

Title: Evaluation of the Margin of Safety and the Local Tolerance of Ciclesonide Delivered per Inhalation via a Specific Equine Inhalation Device in Horses (Study No. 2015008)

Study Dates: August 5, 2016 to December 20, 2017

Study Location: Parma, ID

Study Design:

Objective: A masked, 1-month inhalation safety study was conducted in accordance with Good Laboratory Practice (GLP) Regulations. The objective of this study was to evaluate the margin of safety of ciclesonide when administered via inhalation to horses for 30 days using the final equine inhaler device.

Study Animals: 32 healthy adult horses, 4 to 15 years old, were enrolled. Twenty-four of the horses (12 geldings and 12 mares) were considered average weight with a maximum body weight of 550 kg (range 371.9 kg to 539.8 kg) and eight horses (4 geldings and 4 mares) were considered light-weight with a

maximum body weight of 300 kg (range 121.5 kg to 260.5 kg). Horses were screened prior to enrollment by obtaining nasal swabs for *Streptococcus equi* subsp. *equi* culture, resting adrenocorticotrophic hormone (ACTH) testing, and foot radiographs.

Experimental Design: Horses were randomized into four treatment groups, each receiving a different multiple of the therapeutic dose for 30 days (three times the treatment duration). The treatment groups received 0X (vehicle control), 1X, 2X, and 3X the therapeutic dose of ciclesonide, respectively. Each treatment group included a total of 8 horses, six average weight horses (3 males and 3 females) and two light-weight horses (1 male and 1 female). Horses in the control group received the same number of actuations as the highest dose group (3X) from the nasal inhaler device with vehicle only. The study director and all personnel making clinical observations were masked to treatment assignment.

Drug Administration: All treatments were administered via the left nostril of the horse with the nasal inhaler device. The administered dose was not adjusted for body weight, in accordance with the label dosing instructions. Inhalation doses of 0 mcg (0X), 5,488 mcg (1X), 10,976 mcg (2X), and 16,464 mcg (3X) per day were administered for 15 days, followed by inhalation doses of 0 mcg (0X), 4,116 mcg (1X), 8,232 mcg (2X), and 12,348 mcg (3X) per day for the next 15 days. These daily dosing regimens were accomplished with multiple dosing periods as outlined in Table III.1. Dosing was reduced in the second half of the study to reflect the decrease in total daily dose and frequency after the first 5 days of treatment, as described on the label.

Table III.1. Dosing Schedules

Treatment Group	Study Days	Number of Dosing Periods	Number of Actuations/Period	(Number of Dosing Periods)/Time	Total Number of Actuations* /Day
1 (0X)	Day 0-14	4	12	(2) AM and (2) PM	48
2 (1X)	Day 0-14	2	8	(1) AM and (1) PM	16
3 (2X)	Day 0-14	2	16	(1) AM and (1) PM	32
4 (3X)	Day 0-14	4	12	(2) AM and 2 (PM)	48
1 (0X)	Day 15-29	3	12	(3) AM	36
2 (1X)	Day 15-29	1	12	(1) AM	12
3 (2X)	Day 15-29	2	12	(2) AM	24
4 (3X)	Day 15-29	3	12	(3) AM	36

*Each actuation delivered approximately 343 mcg ciclesonide; in the control group, each actuation delivered the same volume of vehicle only.

Measurements and Observations: Animals were evaluated daily for changes in clinical signs and food and water consumption. Physical examination, body weight measurement, hematology, and clinical chemistry including cortisol and coagulation profile were conducted during acclimation, at Day 14 (± 1 day), and at Day 29 (± 1 day). Urine collection for urinalysis and visual fecal observation occurred during acclimation and at Day 29 (± 1 day). At the conclusion of the study, horses were euthanized and necropsied for organ weights, pathology, and histopathology, including upper and lower airways.

Statistical Methods: The individual horse was considered the experimental unit. Results from the average weight group of horses were subject to statistical analysis. Results from the light weight group of horses were summarized as appropriate, but no hypothesis testing was conducted due to the small sample size ($n=2$ per group). Both continuous and categorical variables were analyzed. Unless otherwise indicated, statistical significance was evaluated at $\alpha = 0.10$. Pairwise comparisons of each ciclesonide-treated group against control using linear contrast were performed at an unadjusted $\alpha = 0.10$.

Continuous outcomes measured only once during the study were evaluated using an analysis of variance model with treatment, sex and sex-by-treatment terms as fixed effects.

Continuous variables measured at multiple times during the study and with a pre-treatment value were analyzed using a repeated measures analysis of covariance, with the last available pre-treatment value used as a covariate. Each repeated measures model contained classification variables "treatment", "day", and "gender"; the two-way interactions "treatment-by-day", "treatment-by-gender", and "gender-by-day"; and the three-way interaction "treatment-by-gender-by-day" as fixed effects.

Results: Clinical Observations: Abnormal observations documented during the study included nasal discharge that varied from serous to mucoid, with occasional cough. Abnormal nasal discharge was observed in all treatment groups, including the control group, and did not appear to increase after treatment. Due to the nasal administration of the test article, nasal discharge could be related to use of the nasal inhaler device. However, there were no clear dose-dependent trends suggesting an effect of ciclesonide.

Facial asymmetry or deviation of the muzzle was observed in two ciclesonide-treated horses during the study (1 horse in the 2X group and 1 horse in the 3X group, both average weight). This finding resolved in one horse prior to the study conclusion. No other related abnormal signs were observed, and no pathologic findings were correlated with this abnormality. Due to the placement of the device in the nostril, this deviation of the muzzle or facial asymmetry may be due to the use of the nasal inhaler device; however, clinical relevance is unknown as it appeared to be transient or temporary.

Clinical Pathology: Cortisol levels, which serve as a marker for suppression of the hypothalamic-pituitary-adrenal axis by systemic action of corticosteroids, were not statistically significantly different between ciclesonide-treatment groups and

the control group. However, two light-weight horses in the 3X treatment group had values (16.3 and 14.1 ng/mL) that were lower than any other values recorded in the study (including baseline values and values from control horses), and lower than the normal reference range (27.6-73.2 ng/mL) on Day 14 (the end of the twice daily treatment period). At Day 29, one horse's cortisol value returned to within the reference range (55.9 ng/mL) and the other remained low (15.9 ng/mL). These reductions in cortisol values in the smallest horses in the highest dose group may represent cortisol suppression from corticosteroid administration; however, clinical relevance is unknown, as neither of these horses had adverse events attributable to administration of ciclesonide.

Sorbitol dehydrogenase levels were not statistically significantly different between ciclesonide treatment groups and the control group. However, 1 control horse (Day 14, SDH 13.6 U/L), 2 light-weight horses in the 3X treatment group (Day 29, SDH values of 10.4 and 8.8 U/L), and 1 light-weight horse in the 2X treatment group (Day 29, SDH 9.3 U/L) that were above the reference range (reference range 1-8 U/L). These values did not correspond with increases in other liver enzymes and the horses remained clinically normal.

Nasal fungal cultures: Fungal cultures (nasal swab) were assessed only categorically (positive or negative), and results did not provide a quantitative assessment of fungal load. In general, for the 0X, 2X, and 3X groups, the number of different fungal species isolated increased by Day 30; however, the result may have been an effect of extended time in the barn with direct contact with other horses and the environment rather than related to treatment with the inhaler. One horse cultured *Candida* species post-treatment, and that horse had no abnormal clinical signs.

Conclusions: The 30-day margin of safety study demonstrates the safety of Aservo[®] EquiHaler[®] in adult horses when administered according to the label dosing regimen, up to 10 days of treatment. Treatment-related effects were minimal. Two light-weight horses in the highest dose ciclesonide-treatment group (3X) had evidence of cortisol suppression, with no associated clinical abnormalities.

B. Pharmacokinetic Study

Objective: To support the use of a single 1X fixed dose per horse regardless of body weight by comparing drug exposure in average and light-weight horses, a separate pharmacokinetic study was conducted to compare the pharmacokinetics of four different dosing regimens in 6 average weight horses (509-611 kg) and 6 light-weight horses (282-381 kg).

Experimental Design: Each horse received the following dosing regimens administered using the nasal inhaler device:

- Period 1: 12 actuations (4116 mcg ciclesonide/horse) as a single inhalation administration,
- Period 2: 16 actuations (5488 mcg ciclesonide/horse) as a single inhalation administration,

Period 3: 8 actuations (2744 mcg ciclesonide/horse) twice a day for 4 consecutive days and once on the fifth day,

Period 4: 8 actuations (2744 mcg ciclesonide/horse) twice a day for 5 consecutive days followed by 12 actuations (4116 mcg ciclesonide/horse) once a day for 5 days.

Measurements: Blood samples were collected at pre-dose, 0 minutes, 5 minutes, 15 minutes, 30 minutes, and 1, 2, 4, 6, 8, 10, 12, and 24 hours after a single inhalation of 2744, 4116, and 5488 mcg in periods 1, 2, 3, and after multiple doses of 2744 and 4116 mcg in Periods 3 and 4. Urine samples were collected at 24 and 48 hours in Period 4. Plasma and urine samples were analyzed for ciclesonide and des-ciclesonide concentrations using a validated liquid chromatograph/mass spectrometry method.

Results: Ciclesonide was rapidly metabolized to des-ciclesonide; there were quantifiable concentrations of des-ciclesonide in most horses at 5 minutes post-dose. Urine concentrations of ciclesonide and des-ciclesonide were below the limit of quantification at 24 and 48 hours after 2744 mcg twice a day for 5 days followed by 4116 mcg once a day for 5 days. Table III.2 summarizes the results of the pharmacokinetic analysis for des-ciclesonide in average and light weight horses (adjusted for body weight) after inhalations of 2744 mcg ciclesonide twice a day for 5 days followed by inhalations of 4116 mcg ciclesonide once a day for 5 days.

Table III.2. Mean (\pm standard deviation; SD) pharmacokinetic parameters of des-ciclesonide after inhalations of 2744 mcg ciclesonide twice a day for 5 days followed by inhalations of 4116 mcg ciclesonide once a day for 5 days

Parameter	Dose (mcg)	Average Horse	Light Horse
C _{max} (pg/mL)	2744	232.67 (40.89)	297.00 (92.0)
T _{max} (hrs) [†]	2744	0.50 (0.5-0.5)	0.50 (0.25-1.0)
AUC _{last} (hr*pg/mL)	2744	824.26 (81.77)	1087.07 (137.85)
t _{1/2} (hrs)	2744	5 (1.06)	5.94 (2.12)
C _{max} (pg/mL)	4116	297.50 (104.62)	493.00 (248.27)
T _{max} (hrs) [†]	4116	0.50 (0.5-1.0)	0.50 (0.5-1.0)
AUC _{last} (hr*pg/mL)	4116	1011.39 (291.72)	1550.31 (690.02)
t _{1/2} (hrs)	4116	6.08 (2.42)	9.75 (4.20)

C_{max}= maximum plasma concentration

[†]T_{max}= time to maximum concentration; median (range)

AUC_{last}= area under the concentration vs time curve to the last quantifiable concentration

t_{1/2}= half-life

Conclusions: Although there was a higher and more variable drug exposure in the light-weight horses compared to the average weight horses, the lack of clinical findings in the Target Animal Safety study supports the overall safety of

Aservo® EquiHaler® in light-weight horses. For des-ciclesonide in both average and light-weight horses, there was a greater than dose proportional increase in C_{max} and AUC_{last} with an increase in dose from 2744 to 4116 mcg, after a single dose. There was minimal accumulation of des-ciclesonide after inhalations of 2744 mcg twice a day for 5 days followed by inhalations of 4116 mcg once a day for 5 days.

C. Field Safety Information:

Additional field safety information was provided from the pilot studies described under section II.A. of this summary (Dosage Characterization). Three horses in pilot study 2012053 treated with ciclesonide at doses of 1687.5 mcg ciclesonide twice daily or 2700 mcg ciclesonide twice daily developed unilateral or bilateral ocular discharge during the study; one of these horses developed ocular discharge twice, once after treatment with either dose. Two horses in pilot study 2013184 developed hypercortisolemia subsequent to treatment with ciclesonide; one of the horses exhibited cortisol suppression prior to developing hypercortisolemia. No clinical effects were associated with hypercortisolemia in affected horses. One horse in study 2014108 developed stomatitis (red mucous membranes) subsequent to treatment with ciclesonide; no clinical effects related to stomatitis (e.g. dysphagia, inappetence, ptyalism) were observed in this case.

IV. HUMAN FOOD SAFETY

This drug is intended for use in horses. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

The product labeling contains the following Warning statement: Do not use in horses intended for human consumption.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Aservo® EquiHaler®:

Not for use in humans. Keep this and all medications out of the reach of children. In case of accidental inhalation, seek medical advice immediately and show the package insert or the product label to the physician.

People with known hypersensitivity to ciclesonide or any of the excipients should avoid contact with Aservo® EquiHaler®.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Aservo® EquiHaler®, when used according to the label, is safe and effective for the management of clinical signs associated with severe equine asthma in horses.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose severe equine asthma, and monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

Aservo[®] EquiHaler[®], as approved in our approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first time we are approving this active ingredient in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA website.