Approval Date: May 11, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-973

B. Sponsor

Boehringer Ingelheim Vetmedica, Inc.
2621 North Belt Highway
St. Joseph, Missouri 64506-2002

C. Proprietary Name

VENTIPULMIN® SYRUP

D. Established Name

clenbuterol hydrochloride

E. Dosage Form

Ventipulmin is a syrup containing 72.5 mcg of clenbuterol hydrochloride per mL.

F. How Supplied

100, 220 and 330 mL bottles

G. Dosage Regimen

Administer orally twice a day (b.i.d.). Initial dose is 0.5 mL per 100 pounds body weight (0.8 micrograms per kilogram) twice daily. Dosage schedule: Initial dosage: 0.5 mL per 100 pounds (0.8micrograms per kilogram) for 3 days (6 treatments); If no improvement, administer 1 mL per 100 pounds (1.6 micrograms per kilogram) for 3 days (6 treatments); If no improvement, administer 1.5 mL per 100 pounds (2.4 micrograms per kilogram) for 3 days (6 treatments); If no improvement, administer 2.0 mL per 100 pounds (3.2 micrograms per kilogram) for 3 days (6 treatments); If no improvement, horse is non-responder to clenbuterol and treatment should be discontinued.

Recommended duration of treatment at effective dose is 30 days. At the end of the 30-day treatment period, drug should be withdrawn. If signs return, the 30-day treatment period may be repeated. If repeating treatment, the step-wise dosage schedule should be repeated.

H. Route of Administration

For oral administration only

I. Indication

Ventipulmin® Syrup (clenbuterol hydrochloride) is indicated for use in the management of horses affected with airway obstruction, such as occurs in chronic obstructive pulmonary disease (COPD).

II. EFFECTIVENESS

A. Dose justification: A dose titration study was conducted

1. Investigator:

   Deborah F. Erichsen, DVM, MS
   Boehringer Ingelheim Animal Health, Inc.
   St. Joseph, Missouri 64502

2. Purpose: To determine the dose-response relationship and the upper limit of a therapeutic dose range of Ventipulmin Syrup alone in the management of COPD in horses.

3. Materials and Methods

   i. Test Animals: Five (5) mature mares and geldings with chronic obstructive pulmonary disease (COPD). COPD horses were identified on the basis of physical examination, response to moldy hay exposure and medical history. COPD horses considered for the trial demonstrated a marked maximum difference between peak inspiratory and peak expiratory intrapleural pressure expressed in centimeters of water (MDPP) response to intravenous atropine at a dosage of 8.8 mcg per kg.

   ii. Study design: A four-period crossover design using five horses with chronic obstructive pulmonary disease (COPD) treated orally twice daily with Ventipulmin Syrup. Each horse served as its own control in accordance with Section 21 CFR 514.111(a)(5)(ii)(a)(2)(iii). The measurements of interest were objectively collected and therefore the need for masking was eliminated.

   iii. Measurements: The MDPP was monitored using the esophageal balloon technique.

   iv. Treatment groups: Horses were treated orally, twice daily, with 0.0, 47.6, 95.2 and 190.4 mcg per mL clenbuterol HCl in accordance with the trial design. This provided for the requirement of administering the various dosage levels at a constant volume per 100 pounds of body weight throughout the study. The marketed product contains 72.5 mcg of clenbuterol HCl per mL.

   v. Test Duration: Each horse was treated with each of the four dosages (0.0, 1.6, 3.2 and 6.4 mcg per kg) over four treatment periods. Each treatment period consisted of a 3-day pretreatment baseline observation and 6 days of twice daily treatment at the scheduled

dosage, with a minimum 96-hour washout between periods, for a complete crossover of doses in each animal.

4. Results: Data obtained from this study indicated a significant linear dose response with progressive improvement in response as dose increased. The data were analyzed using an analysis of variance design for crossover studies. The data support a linear dose response from 1.6 to 6.4 mcg/kg body weight of Ventipulmin Syrup for treatment of COPD in horses (P = 0.0111).

5. Adverse Drug Responses: Clinical adverse drug responses effects, such as sweating, muscle tremor and nervousness, occurred at all dose levels and increased in intensity and frequency of occurrence as the dosage increased. Such side effects were observed to be mild and transient when horses were dosed under the recommended regimen of individual incremental dose titration to effect.

6. Conclusions: The adverse side effects limit the dosage to 3.2 mcg/kg body weight. The information supports a dose of 3.2 mcg per kg body weight of Ventipulmin Syrup for treatment of COPD in horses.

B. Dose Confirmation/Clinical Efficacy

1. Investigators:

   Dr. Ralph E. Beadle
   School of Veterinary Medicine
   Louisiana State University
   Baton Rouge, LA 70803

   Dr. Doyne Hamm
   RAH, Inc.
   Rt. 3, Box 203, Hunt Lane
   Fayetteville, AR 72701

2. Purpose of Study: To confirm the efficacy of Ventipulmin Syrup over an incremental dose range of 0.8 to 3.2 mcg per kg in the treatment of horses with COPD. In addition, the study was used to identify the correlation between a proposed numerical scoring system to be used in the clinical field trial, and the MDPP.

3. Materials and methods

   i. Test Animals: Test animals were clinically diagnosed to have COPD or SPA-COPD [SPA,summer pasture associated]. Test animals were identified as having COPD based on their response to daily exposure to moldy hay or summer pasture exposure [SPA (summer pasture associated)-COPD]. Horses with pneumonia, strangles, influenza or other respiratory or systemic diseases were not eligible for study. Each horse was injected intravenously with 8.8mcgperkilogram atropine to demonstrate the ability of the lungs to respond to bronchodilation. Intrapleural pressures were monitored daily for a minimum of 3 days to establish a baseline. Approximate MDPP was required to be greater

than 12 centimeters of water on 3 consecutive baseline days before treatment was initiated. The severity of COPD was evaluated on a clinical basis at the same time the pleural pressures curves were being recorded for each observation to determine the clinical overall heaves rating (OHR).

ii. Study Design: Sixteen horses were used for the study. Eight horses were paired and each of these 4 pairs were used twice. The other 8 horses were paired, and used once. This procedure is acceptable based on an assumption that a residual effect of replicate treatment is unlikely based on a minimum 50-day-washout period between replications, and a T1/2 of 10.4 h (± 2.25 SD) for clenbuterol (Kallings P., J Vet Pharmacol 1991;14:243-249). The treatments were not known by the investigators until the study was completed, i.e. the study was masked to treatment.

Horses were assigned to pairs based on severity of the COPD condition, i.e., horses with similar degree of heaves were paired together. The assignment of each horse within the pair to Ventipulmin Syrup or placebo treatment was determined from a table of randomized treatments. One horse in each pair received placebo syrup and one received Ventipulmin syrup. Oral syrup containing 72.5 mcg/mL concentration of clenbuterol HCl as intended for marketing and a placebo syrup were used.

iii. Dosages: All test horses were administered coded test product every 12 hours for three days (6 treatments) beginning at the low dose of 0.5 mL per 100pounds body weight (0.8 mcg per kg clenbuterol). Each horse was titrated incrementally to its responsive dose up to a maximum of 2.0 mL per 100pounds body weight. Once the responsive dose was found (MDPP < 60% of mean baseline on the third day of treatment), treatment at that dose was continued for 7 more days for a total of 10 treatments at the responsive dose.

iv. Test Duration: Each test period consisted of a 3-day baseline, a 3-day segmented dose titration of test drug to effect with a 7-day, twice daily total treatment period (if a response dose was obtained), and a minimum 50-day-washout period.

v. Pertinent Parameters Measured: The primary parameter measured in the dose confirmation study was success or failure of Ventipulmin treatment compared to placebo control as determined by measured MDPP. Response was calculated as percent of baseline MDPP [Percent baseline MDPP = (treatment MDPP/baseline MDPP) x 100]. Individual test animals were classified as either responders or non-responders. Responders were those horses that maintained a percent of baseline MDPP less than or equal to 60% for treatment Days 4 through 10 at any of the four incremental dosages (0.5, 1.0, 1.5, or 2.0 mL per 100 pounds body weight). Non-responders were those animals that did not maintain a percent of baseline MDPP less than or equal to 60% for the same treatment period.

The severity of COPD was also evaluated on a clinical basis to show the correlation between measured MDPP and observed respiratory effort. The overall heaves rating (OHR) score was a weighted numerical index of the subjective evaluation of the difficulty in breathing as observed by the veterinary clinician. There were five clinical parameters that were scored and then summed at the end of each clinical observation to obtain the OHR score. The parameters scored were expiratory effort, nostril flare, audible wheezing, nasal discharge, and coughing. Expiratory effort was more heavily weighted numerically in the total OHR score in comparison to the other clinical parameters, because expiratory effort most closely reflects the MDPP measurement.

4. Results: Forty-two percent (42%) of the 12 COPD horses treated with Ventipulmin Syrup were responders, with an average percent baseline MDPP of 32%, i.e., an average improvement in MDPP of 68% from baseline. None of the 12 placebo treated horses were responders. A one-sided sign test was used to compare responders and nonresponders for Ventipulmin Syrup and placebo based on the MDPP measurement. The difference between the Ventipulmin and placebo treatment groups was statistically significant (p = 0.03125). See Table1below.

Table 1. Summary of response of horses by treatment in a study evaluating the effects of Ventipulmin Syrup in the treatment of chronic obstructive pulmonary disease.

Treatment	Number of horses treated	Number of responders (%)	Number of Non-responders (%)
Placebo	12	0 (0%)	12 (100%)
Ventipulmin	12	5 (42%)	7 (58%)

In this blinded test, the relationship between the OHR and MDPP measurement for all horses and for each horse was calculated. The same analysis was done for the expiratory effort to MDPP relationship.

The analysis of pretreatment MDPP showed that the horses were adequately assigned to the treatment groups. The study confirmed that the dosing regimen described in the protocol provided a significant response to Ventipulmin treatment. Ventipulmin-treated horses had a 42% (5 out of 12) success rate while placebo-treated horses had a 0% success rate (P=0.03125, one-sided sign test). The relationship between the ORH and MDPP measurement and expiratory effort and MDPP measurement for all horses was examined. For the correlation study, four horses were eliminated completely and one horse had some observations eliminated because of a compromise of subjective and objective measurements. Each horse had multiple measures so the observations were not independent and thus only the simple correlation is presented. A good linear relationship between ORH and MDPP was demonstrated with a simple correlation of 0.832. The expiratory effort/MDPP data provided a simple correlation of 0.791. Thus there was a strong correlation between the OHR/MDPP and the expiratory effort/MDPP data.

There was only 1 horse where there was no agreement between the OHR and MDPP with regard to the decision of a horse being declared a treatment responder versus a nonresponder to treatment. There was 100% agreement between the expiratory effort and MDPP responder/nonresponder decisions.

5. Conclusions: Ventipulmin Syrup produced an improvement in heaves condition in 42% of the COPD horses as determined by measured MDPP and clinical evaluation while none of the placebo horses improved.

6. Adverse Drug Responses: Adverse drug responses were mild and of short duration. Based on 145 observation days, there were 23 observations of mild sweating or dampness (15.9%); 17 observations of wet patches from sweating (11.7%); 26 observations of mild muscle tremor (18%); and 4 observations of anxiety (2.8%).

C. Clinical Field Study

1. Investigators: The following thirty-five (35) investigators, in nine geographical locations, were involved in this study:

Investigators	**Mailing address**
Dr. Beverly Anderhol	R.D. 1, Box 369 Centre Hall, PA 16828
Dr. Ralph E. Beadle Dr. Dennis D. French	School of Veterinary Medicine Louisiana State University Baton Rouge, LA 70803
Dr. Michael J. Betley	4332 Forest Glen Drive Hoffman Estates, IL 60195
Dr. Gary J. Dillon	Cascade Equine Clinic 29450 S.E. Lariat Lane Boring, OR 97009
Dr. Sharon Doolittle Dr. Sarah Horin Dr. Ernest J. Finocchio	New England Horse Care Centre 2205 Providence Pike N. Smithfield, RI 02895
Dr. Ann E. Dwyer	Genesee Valley Equine Clinic 1089 Bowerman Road Scottsville, NY 14546
Dr. Paul Foy Dr. Richard J. Paumer	Animal Clinic 105 West O Street Ogallala, NE 6953
Dr. Ellen J. Imhof	Aurora Veterinary Clinic 46 South Aurora Road Aurora, OH 44202
Dr. Kevin P. Syvrud	Summit Research 8732 Mountain View Road Polson, MT 59860
Dr. Geoffrey W. Tucker	330 W. Dryden Road Freeville, NY 13068
Dr. John W. Schlipf	5551 Delano Road Melamora, MI 48455

Investigators	**Mailing address**
Dr. Lesley J. Smith	Washington State University Dept. of Vet. Clin. Sciences McCoy Hall, Stadium Way Pullman, WA 99164
Dr. John Jagar	RD 3, Box 65 Millbrook, NY 12545
Dr. Lance F. Karcher	12 Hidden Lane Westbury Long Island, NY 11590
Dr. Steven M. Lascher	Adirondack Veterinary Clinic 418 Geyser Road Balston Spa, NY 12020
Dr. Richard F. Lesser Dr. Pamela A. Wilkins	The Equine Clinic of Oakencroft RR 2, Box 235 Ravena, NY 12143
Dr. Scott McAllister	RR 1, Box 369 Centre Hall, PA 16828
Dr. William J. McGinty Dr. Johnnie F. Copeland	Sarasota Equine Associates 1514 Shadow Ridge Road Sarasota, FL 34240
Dr. Joseph G. Merriam Dr. Ellen Ruth Singer Dr. Sarah L. Cochran	Massachusetts Equine Clinic 75 Locust Street Uxbridge, MA 01569
Dr. Daniel R. O'Leary Dr. Charles D. Vail	Littleton Large Animal Clinic 8025 South Santa Fe Drive Littleton, CO 80120
Dr. Helen O. Noble Dr. Robert M. Orcutt Dr. Bryan G. Parrott Dr. Mary M. Patterson	Combined Veterinary Services 447 Boston Road New Meadows Professional Bldg. Topsfield, MA 01983
Dr. Steven E. Rhodes	Blood Red Farm Box 411, Conklingtown Road Goshen, NY 10924
Dr. Frances G. Woodworth	5063 Watson Road Elba, NY 14058

2. Purpose of Study: The purpose of this study was to confirm the clinical safety and efficacy of an incremental dose range of Ventipulmin Syrup in horses with chronic obstructive pulmonary disease (COPD).

3. Materials and Methods

    i. Test Animals: Two-hundred and forty-one (241) horses, two years of age and older, of either sex and any breed (except pony breeds, i.e. Shetland, Welsh, Connemara, etc.), with a history of COPD were enrolled into the study. Horses in an active breeding program (i.e., brood mares or breeding stallions) were not used in the study.

    ii. Study Design: Horses were individually titrated to their effective dose. Response was determined by the clinical evaluation of the heaves

condition based on an overall heaves rating (OHR).

iii. Diagnosis and study criteria: Determination of COPD was based on evaluation of five clinical parameters which included expiratory effort, nostril flare, audible wheezing, nasal discharge, and coughing. The primary clinical parameter, expiratory effort, was maximally weighted in the scoring system by making the OHR category identical to the expiratory effort category. The OHR categories for the scoring system were defined as follows:

0 = not heavey

1 = slightly heavey

2 = moderately heavey

3 = markedly heavey

4 = severely heavey

The only deviations from the OHR category being the same as the expiratory effort category were as follows:

1. The OHR might be increased 1 category above the expiratory effort score if the nostril flaring score and the wheezing score were both at least 2 categories higher than the expiratory effort score, or
2. the OHR might be decreased 1 category below the expiratory effort score if the nostril flaring score and the wheezing score were both at least 2 categories lower than the expiratory effort score.

Each horse was required to have a minimum of two equal baseline OHR scores of "slightly heavey" or greater and demonstrate a marked clinical improvement in response to intravenous atropine to be accepted into the study. The intravenous atropine test was given to determine reversibility of bronchospasm. Horses were not allowed concomitant bronchodilator therapy within ten days of the atropine test nor during the course of the study. Horses with respiratory diseases, other than COPD, and horses with other systemic diseases were not eligible for the study.

iv. Assignment to treatment group: Horses were assigned to one of two treatment schedules by a random distribution schedule provided to each investigator. Horses on Schedule A were treated for a 10 day period at the effective dose. Treatment was then withdrawn and the COPD condition monitored over an 8-day washout period. Schedule B horses were treated for a total of 30 days at the effective dose with no washout monitoring at the end of the treatment period.

v. Type of Control Group: Each animal served as its own control. The study design in accordance with Section 21 CFR

514.111(a)(5)(ii)(a)(2)(iii) allowed for assessment of the drug effects independent of other variables.

vi. Dosage: The oral syrup, as intended for marketing, was administered orally at doses of 0.8 mcg per kg, 1.6 mcg per kg, 2.4 mcg per kg, and 3.2 mcg per kg, for 10 or 30 days at the effective dose level for each horse. Schedule A treatment was a 10-day duration with a washout period of 8 days. Schedule B treatment was a 30-day duration with no washout period (see table 2).

4. Results: A total of 241horses were eligible and enrolled in the study. Two horses died of non-drug related causes before reaching a responsive dose. Fifty-seven (57) horses responded when treated with 0.8 mcg per kg, 55 responded when titrated with 1.6 mcg per kg, 40 responded when titrated with 2.4 mcg/kg, and 28 responded when treated with 3.2 mcg/kg, while 59 horses did not respond to treatment (see table 2).

   The average response of horses on Schedule A was improvement in the COPD condition while on test drug, with a worsening of the condition after drug withdrawal. Horses on Schedule B demonstrated an overall improvement in the COPD condition while on test drug. See Table 2 below for improvement in COPD condition based on OHR evaluation:

   Table 2. The average Baseline Overall Heaves Rating (BOHR) and Overall Heaves Rating (OHR) by treatment with Ventipulmin. Schedule A is 10 days of treatment with a washout period of 8 days. Schedule B is 30days of treatment with no washout.

				OHR				
Dose (mcg/kg)	**Schedule**	**No. of horses**	**BOHR**	**Day 3**	**Day 10**	**Washout Day 11 to 18**	**Day 20**	**Day 30**
0.8	A	34	2.00	0.79	0.68	1.41		
0.8	B	23	1.87	0.70	0.48		.048	0.61
1.6	A	29	2.03	0.83	.055	1.68		
1.6	B	26	2.08	0.85	0.69		.088	.072
2.4	A	20	2.05	0.80	0.75	1.63		
2.4	B	20	2.20	1.15	1.05		1.37	0.88
3.2	A	15	2.60	1.47	1.47	2.53		
3.2	B	13	2.62	1.38	1.31		1.31	1.62
Non-responder		59	2.39	2.40	3.00			

   Horses which showed an improved overall heaves rating over the baseline after one of the dosing levels above were termed Responders. If a horse did not show an improvement over the baseline after receiving 3.2 mcg/kg for 3 days, or maintain the improvement from day 3 through day 10 at 3.2 mcg/kg, it was considered a Nonresponder. One hundred eighty (180) horses out of a total of 239 were Responders.

Improvement in the COPD condition of horses treated with Ventipulmin Syrup was demonstrated by the OHR scoring system which has been shown to correlate well with the objective MDPP measurement for the determination of severity of heaves and response to treatment. The average improvement from baseline OHR of responders over all doses was 1.31 categories on day 10.

5. Conclusions: Ventipulmin Syrup was shown to be safe and effective for management of COPD in horses when used according to the recommended regimen of incremental dose titration to effect.

6. Adverse Reactions: Clinical side effects, such as sweating, muscle tremor and attitude change, were of low intensity, occurred at all dose levels and were transient under the conditions of recommended use.

III. TARGET ANIMAL SAFETY

A. Target Animal Safety

1. Investigator:
Philip Geeding, DVM
Boehringer Ingelheim Animal Health, Inc.
Research Farm
Cosby, MO 64436

2. Purpose: The purpose of the study was to evaluate the safety of VentipulminSyrup at the recommended dosage levels of 0.8, 1.6, 2.4, and 3.2mcg per kg of clenbuterol HCl for a period of 90 days. It was previously documented that doses above 3.2mcgperkg clenbuterol HCl resulted in unacceptable side effects.

3. Materials and methods

i. Test animals: Thirty (30) normal mares and geldings of various saddle-horse breeds, from 3- to 15-years of age, were randomly assigned to 5 treatment groups, at 6 horses per group. Horses were deemed acceptable on the basis of three pretrial physical examinations, and CBC and serum chemistry analyses of blood samples that indicated the values were within normal limits.

ii. Group assignment: Assignment of horses to the 5 treatment groups was performed using a random distribution table.

iii. Treatments and groups: Ventipulmin Syrup was administered twice daily at oral dose rates of 0.0 mcg per kg (0.0 mL per 100 lbs body weight), 0.8mcgper kg (0.5mL per 100lbs body weight), 1.6 mcg per kg (1.0 mL per 100 lbs body weight), 2.4mcg per kg (1.5mL per 100lbs body weight), 3.2 mcg per kg (2.0mLper100 lbs body weight) of clenbuterol HCl for 90 days, followed by a 14-day washout period.

iv. Pertinent parameters measured: The determination of the long term effects of administration of Ventipulmin Syrup was based on physical

examination, clinical evaluation, and assessment of CBC and serum chemistry. The results from the analysis of blood samples collected at pre-treatment Days 21, 7, and 0 were used as baseline values for comparison to subsequent treatment values. Horses were weighed at Day 0 to calculate initial dosage, then approximately every 30 days until the end of the study to monitor the body condition and to calculate the test product dosage. Gross pathology and histopathology examinations were done on all animals between 1 and 7 days beyond study completion. The horses were randomly clustered for consecutive days of necropsy, since not all animals could be necropsied on the same day. Each cluster contained individuals from all treatment groups.

4. Results: Doses of 0.8 to 3.2 mcg per kg of clenbuterol HCl for 90 days were not associated with clinically relevant changes except for intermittent elevation of serum creatine kinase (CK). No other hematological or clinical parameters demonstrated an effect due to drug. Gross pathology and histopathology evaluations revealed no drug associated lesions.

5. Conclusion: Ventipulmin Syrup at the label-recommended dosages was shown to be safe for use in horses.

IV. HUMAN FOOD SAFETY

A. Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. Clenbuterol is prohibited from extralabel use in food producing animals (21 CFR 530.41(b)).

B. The product labeling carries the following statements:

1. "For use in horses not intended for food."

2. "Federal (U.S.A.) law prohibits the extralabel use of this drug in food animals."

3. HUMAN WARNINGS: This product is not for human use or for use in animals intended for food. Keep out of the reach of children. In case of accidental ingestion, contact a physician immediately. Ingestion of Ventipulmin Syrup may cause undesirable reactions. Clenbuterol, like other beta adrenergic agonists, can produce significant cardiovascular effects in some people as evidenced by elevated pulse rates, blood pressure changes and/or ECG changes.

V. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of section 512 of the Federal Food Drug and Cosmetic Act and section 514 of the implementing regulations. The data indicate that Ventipulmin® Syrup (clenbuterol hydrochloride), when used under labeled conditions, is safe and effective. The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical for the diagnosis

of chronic obstructive pulmonary disease (COPD) in horses and for the safe use of the product. Federal law prohibits the extralabel use of this drug in food animals.

Under section 512(c)(2)(F)(i) of the FFDCA, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of approval since no active ingredient of the drug (including any ester or salt of the active ingredient) has been approved in any other application.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.