**Approved: Nov 16 2001**

# FREEDOM OF INFORMATION SUMMARY

# NEW ANIMAL DRUG APPLICATION
# NADA 141-180

## TORPEX™
## (AEROSOL ALBUTEROL SULFATE)

**"For the immediate relief of bronchospasm and bronchoconstriction associated with reversible airway obstruction in horses."**

**Sponsored by:**

**Boehringer Ingelheim VetMedica, Inc.**

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## I. GENERAL INFORMATION:

NADA Number: 141-180

Sponsor: Boehringer Ingelheim VetMedica, Inc.
2621 North Belt Highway
St. Joseph, Missouri 64506-2002

Generic Name: Albuterol sulfate

Trade Name: Torpex™

Marketing Status: Rx: U.S. Federal Law restricts this drug to use by or on the order of a licensed veterinarian.

## II. INDICATIONS FOR USE:

For the immediate relief of bronchospasm and bronchoconstriction associated with reversible airway obstruction in horses.

## III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE:

Dosage Form: Aerosol albuterol sulfate is formulated with HFA-134a propellant in a Metered Dose Inhaler (MDI) canister. Each canister contains sufficient drug to provide 200 actuations (puffs) to the horse. Each actuation (puff) of the canister valve releases 120 micrograms (μg) drug from the valve.

Route of Administration: Intranasal.

Dosage and Administration: Each actuation (puff) of the device delivers 120 μg of aerosol albuterol sulfate. One dose is three (3) puffs, totaling 360 μg. Administer one dose. If the desired clinical effect is not achieved, one dose may be repeated immediately for a total of six (6) puffs. Do not administer more frequently than every six (6) hours. Do not administer more than 4 treatments within 24 hours. Do not use for more than five (5) consecutive days. In most bronchoconstricted horses, the minimum duration of effect from a single treatment (3-6 puffs) of drug is one hour, but effects may persist for up to seven (7) hours.

## IV. EFFECTIVENESS:

1. DOSE TITRATION/CONFIRMATION STUDY

Title: Aerosol Albuterol Sulfate Dose Titration in Horses with Recurrent Airway Obstruction (ALB-2).

Investigators:
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Pulmonary Laboratory
Department of Large Animal Clinical Sciences
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East Lansing, MI 48824

Purpose: To determine the lowest dose of aerosol albuterol sulfate in HFA-134a propellant that causes clinically significant reduction of airway obstruction, unaccompanied by clinically significant adverse reactions in horses with recurrent airway obstruction.

Test Animals: Ten adult horses (6 mares and 4 geldings) affected by recurrent airway obstruction. Other than respiratory compromise, all horses were in good general health based on physical examination, baseline hemograms and serum chemistries. Each horse had a maximum change in pleural pressure during tidal breathing ($\Delta$Ppl) of greater than 20 cm $H_2O$ prior to each test of the aerosol (drug or placebo).

Treatment groups: Horses were treated once each with 1, 2, 3, or 6 actuations of drug (actuations of the MDI canister corresponding to 120, 240, 360, and 720 micrograms drug) and 6 actuations of aerosol placebo (excipient formulation without drug). A minimum of two days elapsed between treatments.

| Dose Group | Number of actuations (puffs) | Dose ($\mu$g) | Number of horses |
|---|---|---|---|
| placebo | 6 | 0 $\mu$g | 10 |
| 1 | 1 | 120 $\mu$g | 10 |
| 2 | 2 | 240 $\mu$g | 10 |
| 3 | 3 | 360 $\mu$g | 10 |
| 4 | 6 | 720 $\mu$g | 10 |

Study design: The horses were randomized to receive each of the five study treatments according to a balanced Latin square design. Prior to and 5, 10 and 30 minutes after aerosol administration, a clinical observer recorded heart rate and subjectively rated signs of respiratory compromise and adverse reactions (sweating, muscle tremors, excitation, or increase in heart rate). The clinical observer was unaware of the treatment schedule and the results of pulmonary measurement. The dose schedule was provided only to the aerosol administrator.

Parameters Measured: The esophageal balloon technique (using a lung function computer from Buxco Electronics, Inc) determined $\Delta$Ppl, resistance, and dynamic compliance. Pulmonary function measurements were obtained: 1) prior to aerosol administration to qualify the animal and for a baseline value; and 2) at 5, 10, and 30 minutes after aerosol administration.

Results: Data indicate 3 actuations (360 $\mu$g) of drug produced a statistically significant reduction ($p < 0.05$) of $\Delta$Ppl compared to placebo throughout the 30-

minute test period. There was no added benefit from 6 actuations of drug. Clinical observation scores of respiratory compromise tended to decrease in the 3- and 6- actuation dose groups. All doses improved resistance through 10 minutes compared to placebo. Dynamic compliance increased at all doses at 10 minutes. The data demonstrate that 3 actuations is the lowest effective dose.

Adverse Drug Reactions: No clinically significant adverse drug responses (sweating, muscle tremors, or excitation) were observed.

Conclusions: The data support a dose of 3 actuations (360 micrograms) of aerosol albuterol sulfate for horses with recurrent airway obstruction, which results in no clinically significant adverse drug responses.

2. DURATION OF EFFECT

Title: Aerosol Albuterol Sulfate Dose Titration in Horses with Recurrent Airway Obstruction (ALB-3).

Investigators:

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Purpose: To determine the duration of bronchodilation in horses with recurrent airway obstruction after administration of 360 μg (3 actuations or puffs) and 720 (6 actuations or puffs) μg aerosol albuterol sulfate compared to an aerosol placebo.

Test Animals: Nine adult horses (5 mares and 4 geldings) affected by recurrent airway obstruction. Other than respiratory compromise, all horses were in good general health based on physical examination, baseline hemograms and serum chemistries. Each horse had a maximum change in pleural pressure during tidal breathing ($\Delta$Ppl) of greater than 20 cm $H_2O$ prior to each test of the aerosol (drug or placebo).

Treatment groups:

| Dose Group | Number of Actuations (puffs) | Dose (μg) | Number of Horses |
|---|---|---|---|
| placebo | 6 | 0 | 9 |
| 1 | 3 | 360 | 9 |
| 2 | 6 | 720 | 9 |

Study design: The horses were randomized to receive each of the three study treatments according to a 3 x 3 Latin square design. A clinical observer recorded heart rate and subjectively rated signs of respiratory compromise (nostril flare,

and abdominal effort) and adverse drug reactions (sweating, muscle tremors, excitation, or increase in heart rate) prior to, at 5 minutes, and 1, 2, 3, 4, 5, 6, 7 hours after aerosol administration. The clinical observer was unaware of the treatment schedule and the results of pulmonary measurement. The dose schedule was provided only to the aerosol administrator.

Parameters Measured: The esophageal balloon technique was used to obtain data for ΔPpl, resistance, and dynamic compliance. Pulmonary function measurements were obtained: 1) within 24 hours before and just prior to administration of the aerosol to qualify the animal and for a baseline value; and 2) at 5 minutes and 1, 2, 3, 4, 5, 6, 7 hours after aerosol administration.

Results: Data indicate five minutes after administration of 3 or 6 actuations of aerosol albuterol sulfate, a significant decrease in ΔPpl and resistance and an increase in dynamic compliance occurred when compared to placebo. At the 1-hour measurement, these differences persisted for ΔPpl but not for resistance and compliance. These data indicate bronchodilation achieved with 3 or 6 actuations (puffs) of aerosol albuterol sulfate lasts between 30 minutes and one hour although some individual animals may exhibit clinically significant bronchodilation for up to seven hours

Adverse Drug Reactions: No clinically significant adverse drug reactions (sweating, muscle tremors, excitation, or increase in heart rate) were observed.

Conclusions: Bronchodilation resulting from administration of 3 actuations (360 micrograms) of aerosol albuterol sulfate lasts for at least one hour. A dose of 6 actuations (720 micrograms) does not increase the magnitude nor duration of effect. The data support a dose of 3 actuations (360 micrograms) of aerosol albuterol sulfate for horses with recurrent airway obstruction, which results in no clinically significant adverse drug reactions.

3. DOSE CONFIRMATION/CLINICAL EFFECTIVENESS

Title: Aerosol Albuterol Sulfate Dose Confirmation in Horses with Recurrent Airway Obstruction (ALB-4).

Investigators:

Warwick M. Bayly, BVSc, MS
Melissa T. Hines, DVM, PhD
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Pullman, WA 99164

Purpose: To confirm the effects of administration of aerosol albuterol sulfate in horses affected with recurrent airway obstruction.

Test Animals: Ten adult horses (5 mares and 5 geldings) affected by recurrent airway obstruction. All animals were previously assessed for reversible airway

obstruction. Other than respiratory compromise, all horses were in good general health based on physical examination, baseline hemograms and serum chemistries. Each horse fulfilled the criteria of a maximum change in pleural pressure during tidal breathing ($\Delta$Ppl) of greater than 15 cm $H_2O$ prior to each test of the aerosol (drug or placebo).

Treatment groups:

| Dose Group | Number of Actuations (puffs) | Dose ($\mu$g) | Number of Horses |
|---|---|---|---|
| placebo | 3 | 0 | 10 |
| 1 | 3 | 360 | 10 |

Study design: Treatments were randomized based on a random number generator corresponding to horse numbers. A clinical observer recorded heart rate and subjectively rated signs of respiratory compromise (nostril flare and abdominal effort) and adverse drug reactions (sweating, muscle tremors, excitation, or increase in heart rate), 24 hours and just prior to aerosol administration, and at 5 minutes, and 1, 3, 5, and 7 hours after aerosol administration. The canisters of drug and placebo were coded so all personnel were unaware of the treatment schedule (with one exception noted below). The clinical observer was also unaware of the results of pulmonary measurement after qualifying values were obtained.

Parameters Measured: The esophageal balloon technique was used to obtain data for $\Delta$Ppl, resistance, and dynamic compliance. Pulmonary function measurements were obtained: 1) 24 hours and just prior to aerosol administration to qualify the animal and as baseline values; and 2) at 5 minutes and 1, 3, 5, and 7 hours after aerosol administration.

Results: Data indicated that 3 actuations of drug (360 micrograms) improved respiratory function measurements (calculated as a percentage change from baseline values) at 5 minutes and 1 hour compared to placebo. Resistance values were also lower at 5 minutes compared to placebo. There was no difference in dynamic compliance.

One horse in dose group 1, showed only very mild improvement in respiratory response to 3 actuations of drug. A bronchoalveolar lavage performed on this horse prior to aerosol administration revealed a marked suppurative reaction in the airways. For this animal, the canister code was revealed and the horse received 6 actuations of drug (corresponding to 720 micrograms drug delivered from the canister valve) for the next treatment. A marked improvement was observed with no adverse reactions.

Adverse Drug Reactions: Intermittent trembling was observed both in horses receiving placebo and drug. Trembling was mild at the 5-minute observation and absent at other post-treatment evaluation times.

Conclusions: Data confirm that a dose of 3 actuations (360 micrograms) of aerosol albuterol sulfate provides immediate short-term relief from the clinical signs of recurrent airway obstruction. Although some individual horses may

require a higher dose due to airway secretions, 3 actuations is the recommended initial therapeutic dose. If indicated by lack of response to a 3-actuation dose, the 6-actuation dose effectively results in bronchodilation without clinically significant adverse drug reactions.

4. CLINICAL FIELD TRIAL

Title: Clinical Trial of Aerosol Albuterol Sulfate in Horses (ALB-7).

Investigators/Study Locations:


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Purpose: To evaluate the efficacy of 360 micrograms (3 actuations) aerosol albuterol sulfate administered to horses with reversible bronchoconstriction (associated with small airway disease) compared to no treatment.

Test Animals: Twenty-four adult horses affected by recurrent airway obstruction participated in the study. Ten mares, 12 geldings and 2 stallions of various breeds, ranging in age from 6-24 years, were included in the group. Other than respiratory compromise, all horses were in good general health based on physical examination, baseline hemograms and serum chemistries. Each horse fulfilled the criteria of a maximum change in pleural pressure during tidal breathing ($\Delta$Ppl) of equal to or greater than 15 cm $H_2O$ prior to each test period (drug or no treatment).

Treatment groups: Horses were treated once with either 3 actuations (puffs) of drug (360 $\mu$g) or a no-treatment period. A minimum of 24 hours elapsed between treatments.

Study design: The treatment schedule for the horses was randomized and revealed only to the drug administrator for each site. A clinical observer recorded heart rate and respiratory rate, and subjectively rated signs of respiratory compromise (nostril flare and abdominal effort) and signs of adverse drug reactions (sweating, muscle tremors, excitation, or increase in heart rate), prior to the test period (to qualify the animal and as baseline values) and approximately

15 to 30 minutes after treatment (or no treatment). The clinical observers were unaware of the treatment schedule and the results of pulmonary measurement.

Parameters Measured: The esophageal balloon technique was used to obtain data for pulmonary function. Delta Ppl was recorded at all sites; resistance values were obtained only at the three university sites. Pulmonary function measurements were obtained prior to treatment (to qualify the animal and as baseline values) and approximately 15 to 30 minutes after treatment.

Results: Data indicate 3 actuations of the drug (360 μg) significantly reduced max ΔPpl and resistance compared to baseline and compared to the no-treatment period. There was a statistically significantly greater pre-to-post decrease in ratings of airway obstruction ($p = 0.002$), heart rate ($p = 0.020$), max ΔPpl ($p = 0.001$) and resistance ($p = 0.001$) during the drug period. All horses had a minimum of 20% improvement in respiratory function after drug treatment. The study shows a statistically significant greater pre-to-post decrease in resistance ($p = 0.001$) and max ΔPpl ($p = 0.001$) during the drug period which directly supports the indication of bronchodilation.

Adverse Drug Reactions: Clinical signs associated with adverse drug effects (sweating and excitement) were mild and infrequent, and occurred both before and after the drug and no-treatment periods.

Conclusions: Aerosol albuterol sulfate, at 360 mcg (3 actuations or puffs), significantly improved respiratory function with no clinically significant adverse drug reactions, as determined by subjective and objective measures of respiratory function.

## V. ANIMAL SAFETY:

1. TARGET ANIMAL SAFETY STUDY

Title: Confirmation of the safety of repeated and exaggerated doses of aerosol albuterol sulfate in horses.

Investigator:
Bryan Helsten, BS

Bio-Life Associates, LTD.
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Neillsville, WI 54456-8773

Purpose: To evaluate the safety of repeated, exaggerated doses of aerosol albuterol sulfate administered intranasally four times a day (approximately every six hours) to normal horses for 15 days.

Test Animals: Twenty-four adult horses (12 mares and 12 geldings), from 4 to 13 years of age, were randomly assigned to 4 treatment groups, at 6 per group. All

horses were in good general health based on physical examination, baseline hemograms and serum chemistries.

Treatment groups: Each treatment group consisted of 3 mares and 3 geldings.
Group 1 horses received no treatment (negative control).
Group 2 horses received 6 actuations of drug (720 μg drug) four times a day for 15 days (QID/15)
Group 3 horses received 12 actuations of drug (1440 μg QID/15)
Group 4 horses received 15 actuations of drug (1800 μg QID/15)

Study design: Each day, an observer monitored feed intake, behavior, and general health during an acclimation period. During the test period, the horses were also observed for adverse reactions typically seen with bronchodilators (sweating, trembling, excitation) and any other untoward behavioral reactions. Heart rate and respiratory rate were recorded. During the test period, horses were observed within one hour prior to and approximately 30 minutes after dose administration. If side effects were noted at 30 minutes, the animal was again observed after an additional 30 minutes. The clinical observer was unaware of the treatment group of the animal. During the two-week depuration period (cessation of drug), the horses were observed daily for feed intake, general health, behavior, mortality, and morbidity.

Parameters Measured: At intervals during the study, blood samples were collected for hematology and serum chemistries. On Day 16, two horses were euthanized and necropsied, based on the highest cumulative adverse reaction score. These two horses (one from the mid-dose group, Group 3, and one from high-dose group, Group 4) were matched with two horses from the control group (Group 1) based on age, sex, and weight. A gross necropsy and histopathological examination of lung, trachea, liver, heart, kidneys, and any abnormal tissues were conducted on these four horses. A urinalysis was performed on urine samples collected at necropsy.

Results: Hematologic and blood chemistry parameters revealed no effects attributable to the study treatment. Respiratory rates were generally the same during the pre-dose and post-dose observations for all dosing intervals, and there were no apparent changes due to drug treatment. No lesion seen at gross necropsy or in histopathology resulted from treatment. No treatment-related findings were noted in the urinalyses among the test animals when compared to controls. Data for heart rate revealed a significant difference between the control

(Group 1) and both the mid- and high-dose groups (Groups 3 and 4) for Days 1 through 5 of the test period only.

Adverse drug reactions attributable to drug treatment were noted in eight animals during the first seven days (of 15) of drug treatment (one horse from Group 1; two horses in Group 2; three horses in Group 3; and two horses in Group 4). In these horses, sweating was the only observed adverse reaction. Sweating of various degrees occurred within 30 minutes of drug administration and lasted until the 60 minute observation time. No horse responded consistently by sweating each time after drug administration. The severity appeared to decrease over time. Sweating was not observed in any dose group after Day 7.

Conclusions: Transient sweating was seen in all dose groups, including the recommended dose level when the drug was given over an exaggerated treatment period. Aerosol albuterol sulfate was shown to be safe for use in horses.

## 2 TOLERANCE STUDY

Title: Pilot Study: Observation of Side Effects after Repeated Administration of High Doses of Aerosol Albuterol Sulfate in Normal Horses.

Investigator:

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Department of Large Animal Clinical Sciences
College of Veterinary Medicine
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East Lansing, MI 48824

Purpose: To observe and record the severity and duration of side effects resulting from administration of repeated high doses of aerosol albuterol sulfate to normal horses.

Test Animals: Four adult horses (1 mare and 3 geldings), from 5 to 10 years of age, were included in the study. All horses were in good general health and had no history of prior recurrent airway obstruction.

Treatments:

Horse #1 received 12 actuations (1440 μg) drug every 6 hours for 5 days (QID/5).
Horse #2 received 18 (2160 μg) actuations drug QID/5.
Horse #3 received 24 (2880 μg) actuations drug QID/5.
Horse #4 received 30 (3600 μg) actuations drug QID/5.

Horse #1, in a separate trial, also received 36 actuations (4320 μg), once, to measure cardiovascular parameters.

Study Design: Each day of a five-day test period, a test horse was monitored for the onset and duration of adverse reactions typically seen with a bronchodilator (sweating, trembling, and excitement). Horses were scored before and at 5, 15, and 30 minutes after drug administration. The scoring system was a subjective numerical system (0 to 4). The study was not blinded and began with the lowest dose administered to the first horse, proceeding to the next higher dose level for the next horse, in an incremental method.

Parameters Measured: In addition to recording observations for adverse reactions at four dose levels over five days, an additional trial was performed on one horse (Horse #1) to record heart rate and blood pressure before and at 5, 10, 25, and 30 minutes after a single administration of drug at an exaggerated dose.

Results: Sweating was observed at various intervals during the five-day test period for each horse. Typically sweating scores of 2 (flanks warm and hand wet after stroking flanks) or less were observed. At 30 actuations of aerosol albuterol sulfate QID/5, a sweating score of 2 was most frequently observed. A trembling score of 1 (intermittent trembling of flanks) was also observed occasionally at 30 actuations QID/5. Excitation was never observed in any horse. A single administration of 36 actuations of aerosol albuterol sulfate resulted in no change in systolic or diastolic pressure, but caused a transient increase in heart rate (from 50 to 70 beats/minute) that abated over the next 25-30 minutes.

Conclusions: Administration of aerosol albuterol sulfate at up to 5 times the recommended therapeutic dose of 6 actuations (puffs) is associated with only minimal adverse reactions including sweating, trembling of the flanks, and increased heart rate.

## VI. HUMAN SAFETY:

A. Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of the NADA.

B. The product label carries the following statements:

"Not for use in horses intended for human consumption."
"Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian."

C. Human Warnings. The product label carries the following warning:

Avoid spraying into eyes. Keep out of reach of children. Avoid human inhalation. People with heart disorders, hypersensitivity to aerosol albuterol sulfate, and pregnant or nursing women should contact their physician prior to use of this product. Although uncommon, adverse effects of aerosol albuterol sulfate in humans after therapeutic inhalation may include increased heart rate, irregular heart rhythm, and tremors.
Consult a physician immediately if any of these symptoms develop after accidental human inhalation.

## VII. AGENCY CONCLUSIONS:

The data in support of this NADA comply with the requirements of Section 512 of the Act and Part 514 of the implementing regulations. The data demonstrate that Torpex (aerosol albuterol sulfate) is safe and effective when used under labeled conditions.

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 reversible airway obstruction in horses and for the safe use of this product.

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

| US Patent Number | Expiration Date | Summary Description |
|---|---|---|
| 5,225,183 | July 6, 2010 | The patent covers formulation, composition, and/or method of use. |
| 5,695,743 | July 6, 2010 | The patent covers formulation, composition, and/or method of use. |
| 5,439,670 | July 6, 2010 | The patent covers formulation, composition, and/or method of use. |
| 5,605,674 | February 25, 2014 | The patent covers formulation, composition, and/or method of use. |
| 5,766,573 | July 6, 2010 | The patent covers formulation, composition, and/or method of use. |
| 5,666,948 | September 16, 2014 | The patent claims the drug product and method of use |

## VIII. LABELING (ATTACHED)

a. Package Insert
b. Inhaler Device Label
c. Carton Label
d. Shipper Label