Date of Approval: May 3, 2004

FREEDOM OF INFORMATION SUMMARY

NADA 141-228

BUSCOPAN

N-butylscopolammonium bromide

For the control of abdominal pain (colic) associated with spasmodic colic, flatulent colic, and simple impactions in horses.

Sponsored by:

Boehringer Ingelheim Vetmedica, Inc.

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FREEDOM OF INFORMATION SUMMARY

1. *General Information:*

a.	File Number:	NADA 141-228
b.	Sponsor:	Boehringer Ingelheim Vetmedica, Inc. 2621 North Belt Highway St. Joseph, MO 64506-2002 Drug Labeler Code: 000010
c.	Established Name:	N-butylscopolammonium bromide
d.	Proprietary Name:	BUSCOPAN Injectable Solution
e.	Dosage Form:	Injectable Solution
f.	How Supplied:	50 mL multi-dose vials
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	20 mg N-butylscopolammonium bromide/mL
i.	Route of Administration:	Slow intravenous administration
j.	Species/Class:	Equine
k.	Recommended Dosage:	Single injection of 0.3 mg/kg body weight (0.14 mg/lb) or 1.5 mL/100 kg (45.4 pounds) body weight
l.	Pharmacological Category:	Anticholinergic, antispasmodic
m.	Indications:	BUSCOPAN Injectable Solution is indicated for the control of abdominal pain (colic) associated with spasmodic colic, flatulent colic, and simple impactions in horses.

2. *Effectiveness*

a. Dosage Characterization

Eight ponies with cecal fistulas were evaluated using the cecal balloon model. Two mares and six geldings, ranging from 6-12 years of age, were given a single IV dose (market formulation) of BUSCOPAN. At a dose of 0.30 mg/kg, 6 of 8 animals exhibited decreased pain associated with moderate colic (i.e., reduced total colic score

following BUSCOPAN administration). The effects lasted approximately 26 minutes following BUSCOPAN administration.

Conclusion: Based on the evaluation of colic pain induced in the above model, a dose of 0.3 mg BUSCOPAN / kg body weight was selected for the control of abdominal pain (colic) associated with spasmodic colic, flatulent colic, and simple impactions in horses.

b. Substantial Evidence

Clinical Effectiveness and Safety of BUSCOPAN in Horses (635-0300-98E-004)

(1) Type of Study: Multi-centered field study

(2) Investigators:

Clinic	Investigator(s)
Timber Creek Veterinary Hospital Canyon, TX	Dr. Chris Morrow*; Dr. Gregg Veneklasen; Dr. Terri Teeter
Boulder Valley Veterinary Clinic Longmont, CO	Dr. Martin Butley*; Dr. Dale Bowers
Equine Medical Services Columbia, MO	Dr. Paul Schiltz
Minnesota Equine Associates, LTD Loretto, MN	Dr. W.G. Schroeder
Greene, Lewis, & Associates LLC Covington, LA	Dr. Hunter Lewis*; Dr. Gary Greene
Equine Veterinary Associates Conroe, TX	Dr. James Schulze
At Farm Veterinary Services El Dorado, CA	Dr. James Garfinkel
Bracken Equine Clinic San Antonio, TX	Dr. Robert Ball
Dr. Harry W. Werner N. Granby, CT	Dr. Harry Werner
Eagle Fern Veterinary Hospital PC Estacada, OR	Dr. Justin Edwards
Greentree Veterinary Hospital La Mesa, NM	Dr. John Harlacker
Lazy E Ranch Guthrie, OK	Dr. Joe Noble

Dr. Joe Bertone Carbondale, CO	Dr. Joe Bertone*; Dr. Steve Hardy
University Equine Veterinary Services Findlay, OH	Dr. Rick Henninger*; Dr. Greg Hass
Specifically Equine Veterinary Services Buellton, CA	Dr. Benjamin Bramsen*; Dr. Trish Chism
Midwest Equine Veterinary Service Roanoke, IN	Dr. Diane Finch
Wood River Equine Hospital Bellevue, ID	Dr. Steve Fairbrother*; Dr. Kelly Fredrickson
Central Coast Equine Arroyo Grande, CA	Dr. Shawn Lee

* Primary Investigator

(3) General Design:

(a) Purpose: To demonstrate, in a well-controlled field study, the effectiveness of BUSCOPAN (N-butylscopolammonium bromide) in the control of abdominal pain (colic) associated with spasmodic colic, flatulent colic, and simple impactions.

(b) Test Animals: Two hundred twenty-five horses were evaluated for safety (115 placebo, 110 BUSCOPAN), 217 were evaluated for effectiveness (110 placebo, 107 BUSCOPAN)

(c) Control Drug: The placebo was identical to BUSCOPAN Injectable without the active ingredient

(d) Dosage Form: BUSCOPAN Injectable Solution (final market formulation)

(e) Route of Administration: a single, slow, intravenous injection (jugular)

(f) Dosage: 0.3 mg/kg body weight (0.14 mg/lb)
(1.5 ml/100 kg body weight; 0.68 ml/100 lb body weight)

(g) Test Duration: Thirty minute observation following administration

(h) Variables Measured: A total colic score was assigned to each case based on five individual criteria (pawing, head and body movement, kicking, desire to lie down, and sweating). A general clinical impression was also made at 30-minutes post-treatment. Other ancillary response variables included heart rate, respiratory rate, mucous membrane color, capillary refill time, appetite, rectal exam, behavioral attitude, and borborygmi.

(4) Statistical Analysis:

Continuous variables (heart rate, respiration rate, and total colic score) were analyzed by mixed model, repeated measures analysis of variance. Because sex was not part of the experimental design, and randomization procedures did not account for sex, sex was not included in the model. Factors in the model included treatment, time, and time*treatment as fixed effects, and site as a random effect. Sites with eight or more cases were assigned a "score" of 1, while sites with at least four but fewer than eight cases were assigned a "score" of 0.

For the continuous variables, "pretreatment" with an NSAID or analgesic was examined as a possible covariate. The only variable for which this covariate was retained in the model ($p<0.03$) was respiration rate. Least squares means for respiration rate thus reflect this analysis. For total colic score and heart rate, "pretreatment" was not significant ($p>0.28$ and $p>0.35$, respectively) and was therefore excluded from the statistical model.

For categorical variables, the data were subjected to frequency table analyses using Chi-square or Cochran-Mantel-Haenzel (CMH) probabilities, as appropriate. Pretreatment scores (time "0" or baseline) were used as stratification variables in these analyses. When a significant ($p\leq0.10$) association between a response variable and treatment was observed at pretreatment, the CMH test stratifying for the response variable at pretreatment was used for analyses of the response variable at 5, 15, and 30 minutes post-treatment.

(5) Results:

There were 18 investigators, with a total of 217 cases evaluable for statistical analyses of effectiveness. Horses were randomly assigned to either the BUSCOPAN or placebo group, and investigators were masked with respect to treatment.

Horses underwent a thorough pretreatment colic examination, with follow-up evaluations at 5, 15 and 30 minutes following test article administration. Included in the examination was determination of a "total colic score" based upon evaluation of the various clinical signs of colic. Following the 30-minute examination, investigators provided their "general clinical impressions" of the effectiveness of the test article.

Of the horses used in the study, Quarter Horses, Arabians, and Thoroughbreds accounted for approximately 40%, 14%, and 12% of the cases, respectively. The majority of the horses treated were geldings (53%), followed by mares (39%) and stallions (8%). Body weights ranged from 300-1700 lb (136-772 kg), with a mean weight of 968 lb (440 kg). Ages ranged from 4 months to 35 years, with an average of 10.6 years.

Total colic scores (Table 1) decreased throughout the 30-minutes post-treatment observation period for both BUSCOPAN and placebo. At each time period the

total score was significantly lower ($p \leq 0.001$) for the BUSCOPAN-treated horses.

Table 1. Total Colic Score: Least Squares Means (LSM) and Standard Errors (SEM)

	Pretreatment		Post-treatment					
			5 min		15 min		30 min	
Test article	LSM	SEM	LSM	SEM	LSM	SEM	LSM	SEM
Placebo (P)	**6.7**	0.33	**4.9**[a]	0.33	**4.2**[ab]	0.33	**3.8**[b]	0.34
Buscopan (B)	**6.5**	0.33	**3.1**[a]	0.33	**2.4**[ab]	0.33	**2.1**[b]	0.34
B vs. P			***		***		***	
Number (N)								
Placebo	110		110		109		104	
Buscopan	107		107		107		103	
TOTAL	217		217		216		207	

*** Means in the same column differ significantly ($p \leq 0.001$).
Post treatment means in the same row with different superscripts differ significantly ($p \leq 0.05$), whereas means that share a common superscript do not differ significantly.

The response to BUSCOPAN was also seen in the individual components that were used to arrive at the total colic score. Four of the five components were consistently improved for most of the post-treatment evaluations in the BUSCOPAN group compared to placebo (Table 2).

Table 2. Statistical Results of Post-Treatment Frequency Analyses for Colic Score Component Variables, Comparing BUSCOPAN and Placebo

Variable	Pre-treatment	Post-treatment		
		5 min	15 min	30 min
Sweating	NS	NS	NS	NS
Pawing	NS	$p \leq 0.0333$	$p \leq 0.0402$	$p \leq 0.0041$
Head & body movement	NS	NS	$p \leq 0.0233$	$p \leq 0.0388$
Kicking	NS	$p \leq 0.0072$	$p \leq 0.0152$	$p \leq 0.0021$
Desire to lie down	NS	$p \leq 0.0007$	$p \leq 0.0003$	$p \leq 0.0003$

NS = nonsignificant

The results (%) for the general clinical impressions are presented by treatment group in Table 3. A greater percentage of BUSCOPAN-treated horses were rated as excellent/good/ or moderate, and more placebo cases were rated as poor/not effective ($p<0.0001$).

Table 3. Frequency (%) Distribution of Clinical Impression Responses

Test Article	Excellent	Good	Moderate	Poor	Not Effective	Total
Buscopan	**46**	**25**	**17**	5	7	100
Placebo	20	14	8	**21**	**37**	100

The general clinical impression was statistically analyzed as a binomial variable, where the excellent/good/moderate responses were termed "successes," and the poor/not effective responses were called "failures." This binomial response is presented in Table 4. These results show that the Investigators found BUSCOPAN to be clinically effective in treating spasmodic, flatulent, and simple impaction colic in this study.

Table 4. Frequency (%) of Successes and Failures for General Clinical Impression

Test Article	Buscopan (B)	Placebo (P)	B compared to P
Success	**88**	42	$p \leq 0.0001$
Failure	12	**58**	
Total	100.0	100.0	

The overall improvement in the behavioral attitudes of the horses appeared to be better in the BUSCOPAN-treated cases compared to the placebo cases (Table 5). A significantly higher percentage of horses treated with BUSCOPAN were rated as "alert/calm" at 15 and 30 minutes post-treatment ($p \leq 0.0050$ and 0.0058, respectively). Conversely, a significantly greater proportion of placebo-treated horses were "nervous/restless" ($p \leq 0.006$).

Table 5. Frequency of Responses (%) for Behavioral Attitude

	Pretreatment		Post-treatment					
			5 min		15 min		30 min	
Behavioral Attitude Responses	Buscopan	Placebo	Buscopan	Placebo	Buscopan	Placebo	Buscopan	Placebo
Violent	3	5	2	4	3	3	2	2
Nervous/restless	52	53	**34**	**45**	**14**	**33**	**10**	**26**
Alert/calm	13	15	**44**	**28**	**67**	**46**	**73**	**51**
Drowsy/depressed	32	28	21	24	16	18	16	21
Obtunded/comatose	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total [a]	100	101	101	101	100	100	101	100
Buscopan vs. placebo	NS		NS		$p \leq 0.0050$		$p \leq 0.0058$	

NS = nonsignificant, [a] Not equal to 100% due to rounding.

There were no significant differences ($p \geq 0.25$) between the two treatment groups for mucous membrane color, capillary refill time, and respiration rate. Post-treatment heart rate was significantly elevated ($p \leq 0.0001$) for BUSCOPAN at 5 and 15 minutes, compared to placebo cases (Table 6). By 30 minutes the heart rate for the BUSCOPAN-treated horses did not differ from their pre-treatment values.

Table 6. Heart and Respiration Rates: Least Squares Means (LSM) and Standard Errors (SEM)

	Pretreatment		**Post-treatment**					
			5 min		**15 min**		**30 min**	
Test article	**LSM**	SEM	**LSM**	SEM	**LSM**	SEM	**LSM**	SEM
	Heart Rate							
Placebo (P)	**49.9**	2.98	**49.1**	2.98	**47.8**	2.98	**47.0**	3.00
Buscopan (B)	**50.9**[b]	2.99	**66.1**[a]	2.99	**62.6**[a]	2.99	**53.8**[b]	3.00
B vs. P			***		***		***	
	Respiration Rate							
Placebo (P)	**20.0**	1.17	**19.0**	1.17	**18.6**	1.74	**18.6**	1.20
Buscopan (B)	**21.6**	1.20	**19.3**	1.20	**18.6**	1.20	**17.5**	1.22
B vs. P								

*** Means in the same column differ significantly ($p \leq 0.0011$).
Means in the same row with different superscripts differ significantly ($p \leq 0.0001$).

Responses in borborygmi are believed to reflect the physiological effect of BUSCOPAN on the smooth muscle of the intestines. The intensity and frequency of borborygmi in all four quadrants were generally reduced for the BUSCOPAN group compared to placebo. These reductions were statistically significant ($p \leq 0.02$) for most of the variables, but were less evident for frequency at 30 minutes compared to 5 and 15 minutes (Table 7).

Table 7. Statistical Results of Frequency Analyses for Borborygmi

Variable	Pre-treat.	Post-treatment		
		5 min	15 min	30 min
Left dorsal				
intensity	NS	$p \leq 0.0013\downarrow$	$p \leq 0.0019\downarrow$	$p \leq 0.0076\downarrow$
frequency	NS	$p \leq 0.0002\downarrow$	$p \leq 0.0012\downarrow$	$p \leq 0.0160\downarrow$
Left ventral				
intensity	$p \leq 0.0519\uparrow$	$p \leq 0.0001\downarrow$	$p \leq 0.0001\downarrow$	$p \leq 0.0174\downarrow$
frequency	$p \leq 0.0381\uparrow$	$p \leq 0.0001\downarrow$	$p \leq 0.0001\downarrow$	NS
Right dorsal				
intensity	$p \leq 0.0473\uparrow$	$p \leq 0.0001\downarrow$	$p \leq 0.0003\downarrow$	$p \leq 0.0092\downarrow$
frequency	NS	$p \leq 0.0088\downarrow$	NS	NS
Right ventral				
intensity	$p \leq 0.0209\uparrow$	$p \leq 0.0001\downarrow$	$p \leq 0.0001\downarrow$	$p \leq 0.0003\downarrow$
frequency	NS	$p \leq 0.0049\downarrow$	$p \leq 0.0022\downarrow$	NS

NS = nonsignificant, ↓ decreased or ↑ increased for Buscopan relative to placebo

There was a subset of 37 horses enrolled in this study (37 of the 225) that had previously been treated with NSAIDs (nonsteroidal anti-inflammatory drug) or analgesics. This subset was comprised of 15 BUSCOPAN and 22 placebo horses. The results of the general clinical impressions for this subset (37 cases) are represented in Table 8. The comparison between successes and failures for the treatment groups was significant (p=0.0024). There was a higher success rate for BUSCOPAN compared to placebo. Compared with the results from the overall study (Table 4), the number of successful responses (88% overall and 87% in this subset) for BUSCOPAN-treated horses did not appear to be affected by the previous use of NSAIDs/analgesics.

Table 8. Comparison of Success and Failure Rates (%) for "Pretreated" Cases

Test Article	Buscopan (B)	Placebo (P)	B vs. P
Success	**87**	36	$p \leq 0.0024$
Failure	13	**64**	
Total	100.0	100.0	

(6) Conclusions:

In this study, a single intravenous injection of BUSCOPAN provided control of abdominal pain associated with spasmodic, flatulent, and mild impaction colics for 30 minutes.

(7) Adverse Reactions:

Mild, transient, elevated heart rates and decreased borborygmal sounds were observed over the 30 minute evaluation period following BUSCOPAN injection.

3. Target Animal Safety

a. Dose Tolerance Study (10x)

(1) Type of Study: Target animal safety

(2) Study Director / Study Location: Thomas J. Kennedy, Ph.D.
Boehringer Ingelheim Research Farm
Cosby, Missouri

(3) General Design:

(a) Purpose: This study was conducted to observe the toxicological responses of horses when BUSCOPAN was administered intravenously at a dose of 10x (3.0 mg/kg body weight).

(b) Test Animals:

4 horses (two mares and two geldings) divided into 2 replicates; one replicate slaughtered at 24 hours, and the other replicate slaughtered at 72 hours post injection

3 Quarter Horses, 1 Arab/Quarter Horse cross; ages 8-14 years

(c) Control Drug: not applicable

(d) Dosage Form: BUSCOPAN Injectable Solution (final market formulation)

(e) Route of Administration: a single, slow, intravenous injection (jugular)

(f) Dosage: 3.0 mg/kg body weight (10x)

(g) Test duration: 24-72 hours following a single injection

(h) Pertinent Variables/Observations:

Pretreatment physical examination and blood sampling for CBC, serum chemistry, and blood coagulation

Clinical evaluations at 30 minutes pre-injection; post-injection at 10 minutes and 1, 2, 3, 4, and 24 hours (also 48 and 72 hours for two horses)

Gross pathology and histopathology on two horses (one mare and one gelding) at 24 hours, and two horses (one mare and one gelding) at 72 hours post-dosing

(i) GLP Compliance: This study was conducted in compliance with 21 CFR Part 58.

(4) Results:

Clinical findings: All horses experienced dilated pupils, with the pupillary light reflex returning to normal by 4-24 hours post-injection. Heart rates were elevated post-treatment, but returned to the normal range by 4 hours. Mucous membranes were dry at 10 minutes after treatment, but returned to normal in 1-2 hours.

Horses eliminated normal feces by 3-6 hours post-treatment. Gut motility, as evidenced by frequency and intensity of borborygmi, was inhibited most at 10 minutes, but returned to baseline frequency and intensity by 3-4 hours. Two horses experienced mild colic (at 10 minutes or 11 hours post injection), but both incidences were resolved without medication.

Blood analyses: There were no drug associated changes in CBC, serum chemistry, or blood coagulation.

Gross pathology / histopathology: There were no drug associated changes.

(5) Conclusion:

There were no unexpected or untoward responses to the test article. There were transient changes in pupillary light reflex, heart rate, mucous membrane hydration, and intestinal motility. All responses were well-tolerated, consistent with the drug's expected pharmacology (anticholinergic), and none were considered clinically or pathologically relevant.

b. Target Animal Safety (1x, 3x, 5x)

(1) Type of Study: Target animal safety

(2) Study Director / Study Location: John W. Campbell, Ph.D.
Southwest BioLabs
Las Cruces, New Mexico

(3) General Design:

(a) Purpose: This study of target animal safety was conducted to observe the effects of BUSCOPAN using two different overdosing regimens: 1) a study of 0x, 1x, 3x and 5x the recommended dose (0, 0.3, 0.9, and 1.5 mg/kg body weight) for 3x the time (once a day for 3 consecutive days); and 2) a study of 0x and 1x the recommended dose for 3 successive treatments on the same day (once an hour for 3 consecutive hours).

(b) Test Animals

Eight animals per group, equally divided between males (geldings) and females

Quarter Horses and Thoroughbreds, ages 2-17 years

(c) Control Drug: The placebo was identical to BUSCOPAN Injectable without the active ingredient

(d) Dosage Form: BUSCOPAN Injectable Solution (final market formulation)

(e) Route of Administration: a single, slow, intravenous injection (jugular)

(f) Dosages:

Regimen 1: 0, 0.3 (1x), 0.9 (3x), and 1.5 (5x) mg/kg body weight, administered once per day for three consecutive days

Regimen 2: 0 and 0.3 (1x) mg/kg body weight, administered once per hour for three consecutive hours on a single day

(g) Test Duration: 7 days

(h) Pertinent Variables/Observations:

Physical examinations at 24 hours prior to first treatment, and again 24 hours and 7 days after final treatment

Hematology, coagulation, and serum chemistry on blood samples drawn 7 days and 1 day prior to first treatment, and 24 hours after final treatment

Daily general health observations for 6 days prior to first treatment and 6 days after final treatment

Clinical evaluations (pupillary light reflex, heart rate/rhythm, oral mucous membranes, and auscultated gut activity) conducted 4 hours after each daily treatment, or 1 hour after each hourly treatment, then continued at 4-hour intervals for 24 hours after the final treatment

Gross pathology on one mare and one gelding from each treatment group; histopathology on the control and highest dosage group in each regimen

(i) GLP Compliance: This study was conducted in compliance with 21 CFR Part 58.

(4) Statistical Analyses & Results:

Statistical significance is concluded for p-values ≤ 0.10 in the target animal safety study.

There were no treatment-related findings either at necropsy or upon histopathological examination. All blood-related analyses were within normal ranges.

There were no clinically or statistically significant effects of treatment on either heart or respiration rates detected by repeated measures analysis of covariance. Though a transient effect on heart rate was noted in other studies, observations in this study were made after the primary pharmacological activity for this drug had passed. This study confirms that there are no lasting effects on heart rate, even at dosages up to five times that which is recommended for therapeutic effect.

No statistically significant association of dosage with changes in heart rhythm was found. There was an apparent numerical, though non-dose-related, trend among the BUSCOPAN-treated groups for a slightly higher incidence of second-degree atrioventricular block (AVB) compared to the placebo groups. A closer examination of the data revealed that the total incidence of confirmed AVB after treatment was unchanged from that before treatment. Because AVB is a normal, physiological rhythm in many healthy horses, these findings are considered not to be clinically relevant.

Binary responses were tested for linear trend in dose by means of an exact test. There was no statistically significant association of dosage with pupil / pupillary light response. Dilated pupils were observed as frequently in control groups as they were in BUSCOPAN-treated groups. Pupillary dilation is an expected pharmacological response to this class of drug (anticholinergic). The lack of a clinical response in this study is likely related to the longer time after treatment at which the initial observations were made. In any event, this study shows that any effect on pupillary light response is transient.

Gut motility was assessed by auscultating borborygmi (gut sounds), evaluating both their frequency and their intensity. A reduction in gut motility, without causing gut stasis, is the intended clinical or therapeutic effect of this drug, and can be manifested by reduced intensity and/or frequency.

In the current study, there were isolated (i.e., isolated by location and time) instances of statistically significant ($p \leq 0.10$) associations of dosage with reduced gut motility. Summing these observations across abdominal quadrants and times, it was evident that the primary clinical effect, in keeping with the drug's pharmacological properties, was a reduction in the intensity of gut sounds (see Table 1 below). The total incidence of reduced intensity (% reduced) was numerically increased for most of the BUSCOPAN-treated groups in comparison to the respective controls. This study showed that these effects are transient in that the intensity had returned to baseline levels at the final physical examination. There was no evidence of gut stasis or abdominal pain (colic) among the BUSCOPAN-treated horses, even at levels up to 5x.

Table 1. Incidence of "Reduced" Intensity of Borborygmi [a]

Dose	Group	Regimen	Abdominal Quadrant [b]				Total reduced (%)	Total not reduced	Total # of obser-vations
			LD	LV	RD	RV			
0x	3	1	11	4	5	1	21 (10.9)	171	192
1x	4	1	17	15	11	7	50 (26.0)	142	192
3x	2	1	12	8	5	4	29 (15.1)	163	192
5x	1	1	17	10	9	8	44 (22.9)	148	192
0x	6	2	7	5	6	3	21 (41.2)	30	51
1x	5	2	19	16	8	7	50 (45.9)	59	109

[a] Those with scores of either "weak" or "absent" during and through 24 hours after dosing.
[b] Number of occurrences in each quadrant summed across all post-treatment observations through 24 hours (1 day) after the final treatment.
LD = left dorsal; LV = left ventral; RD = right dorsal; RV = right ventral

There was no influence of BUSCOPAN dose on appetite, either statistically or clinically. At some observation times, there was a statistically significant ($p \leq 0.10$) association of dosage with the frequency of defecation. This was manifested in a reduction in the number of fecal piles compared to the previous observation time. Examination of the data revealed that a large majority of horses with such "decreases" also had decreases at various times prior to treatment. This effect is clinically unimportant in that there was no evidence of gut stasis. Furthermore, at each twice daily observation time there was always fresh feces present.

There were a couple of observation times where the effect on mucous membrane color (MMC) was statistically significant. These events appeared to be incidental and isolated. Evaluation of the total incidence of "pale" MMC demonstrated that this effect had no clinical significance.

(5) Conclusion:

The only clinically relevant finding was a reduced intensity of borborygmi, an effect that is associated with the drug's intended pharmacologic and therapeutic activity. This study demonstrated that BUSCOPAN is safe in horses when administered for three consecutive days at dosages up to five times that which is recommended for its therapeutic indication. It is also shown to be safe when administered at the recommended dose at hourly intervals for up to three hours in a single day.

c. Hemodynamic Effects Study

(1) Type of Study: Target animal safety

(2) Study Directors / Study Location: Robin D. Gleed, DVM
Thomas R. Geimer, DVM
College of Veterinary Medicine,
Cornell University, Ithaca, New York

(3) General Design:

(a) Purpose: This study was conducted to determine the hemodynamic effects of 0.3 mg/kg body weight BUSCOPAN when administered intravenously to adult ponies.

(b) Test Animals: 8 adult ponies, ages 7-13 years, each with a surgically translocated subcutaneous carotid artery

(c) Control Drug: sterile saline solution

(d) Dosage Form: BUSCOPAN Injectable Solution (final market formulation)

(e) Route of Administration: a single, slow, intravenous injection (jugular)

(f) Dosage: 0.3 mg/kg body weight

(g) Test duration: 61 minutes

(h) Pertinent Variables/Observations:

Measured hemodynamic variables included heart rate (HR), cardiac output (CO), systemic arterial blood pressure from the carotid artery (P_{ca}), pulmonary artery pressure (P_{pa}), and right atrial pressure (P_{ra}). Observations were made at -30, -15, 1, 16, 31, and 61 minutes post drug injection.

Calculated variables included stroke volume (SV) and systemic vascular resistance (R_{sys}).

(i) GLP Compliance: This study was not conducted in compliance with 21 CFR Part 58, but was conducted in compliance with Good Clinical Practices (VICH GL 9).

(4) Results:

Compared to saline treatment, BUSCOPAN-treated ponies exhibited a decrease in right atrial pressure, which persisted for at least 61 minutes (final observation). Heart rate was elevated in BUSCOPAN-treated ponies for 31 minutes.

(5) Conclusion:

BUSCOPAN produced measurable changes in right atrial pressure and heart rate, but cardiac output, was maintained. These hemodynamic changes were of little clinical significance, being qualitatively similar to those reported in other studies for low doses of atropine.

4. Human Safety

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human warnings are provided on the label as follows: "Not for use in horses intended for human consumption. Not for use in humans. Keep out of the reach of children. If ingested, contact a physician immediately."

5. Agency Conclusions

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that BUSCOPAN Injectable Solution for horses, when used under the conditions of use, is safe and effective for the control of abdominal pain (colic) associated with spasmodic colic, flatulent colic, and simple impactions.

BUSCOPAN Injectable Solution is restricted to use by or on the order of a licensed veterinarian because professional veterinary expertise is required to determine when a horse has abdominal pain (colic) due to spasmodic colic, flatulent colic, or a simple impaction, and to monitor the animal for signs of adverse reactions.

Under Section 512(c)(2)(F)(i) of the Federal Food, Drug and Cosmetic Act, this approval qualifies for five years of marketing exclusivity beginning on the date of the approval because no active ingredient has been previously approved.

6. Attachments

Facsimile Labeling is attached as indicated below:

1. Package insert
2. Bottle label
3. Carton label
4. Shipper label