I. GENERAL INFORMATION

A. File Number

NADA 140-912

B. Sponsor

Mobay Corporation
Animal Health Division
P. O. Box 390
Shawnee, KS 66201

C. Proprietary Name

Rintal® Tabs Anthelmintic Tablets

D. Established Name

febantel

E. Dosage Form

Tablets - two sizes, one (No. 6, for use in dogs, cats, puppies, and kittens) containing 27.2 mg Febantel/scored tablet and the other (No. 36, for use in dogs, puppies and cats) containing 163.3 mg febantel/scored tablet

F. Dosage Regimen

Dogs and Cats	10 mg febantel/kg body weight given daily for 3 consecutive days.
Puppies and Kittens less than 6 mo. of age	15 mg febantel/kg body weight given on a full stomach daily for 3 consecutive days.
NOTES	See attached labeling (package insert) for complete dosage directions/schedules and appropriate uses for each tablet size.

G. Route of Administration

Oral

H. Species/Class

Dogs and Cats

I. Indication

Rintal® Tabs Anthelmintic Tablets are indicated for the removal of the following nematode parasites:

In Dogs and Puppies:

- Hookworms (Ancylostoma caninum, Uncinaria stenocephala)
- Ascarids (Toxocara canis, Toxascaris leonina)

- Whipworms (Trichuris vulpis)

In Cats and Kittens:

- Hookworms (Ancylostoma tubaeforme)
- Ascarids (Toxocara cati)

II. EFFECTIVENESS

The effectiveness of Rintal® Tabs (febantel) Anthelmintic Tablets is based on a demonstration of bioequivalence of the tablets to Vercom Paste (NADA 133-953). Vercom Paste (containing febantel for nematode control and praziquantel for tapeworm control) is approved in dogs and puppies for removal of hookworms (Ancylostoma caninum, Uncinaria stenocephala,) ascarids (Toxocara canis, Toxascaris leonina), whipworms (Trichuris vulpis) and tapeworms (Taenia pisiformis, Dipylidium caninum). It is also approved in cats and kittens for removal of hookworms (Ancylostoma tubaeforme), ascarids (Toxocara cati) and tapeworms (Dipylidium caninum and Taenia taeniaeformis). Well-controlled studies included in the approved Vercom Paste (febantel + praziquantel) NADA established the dose of febantel at 10 mg/kg/day for 3 days for dogs and cats, and 15 mg/kg/day for 3 days for puppies and kittens fewer than 6 months of age and dosed on a full stomach. These studies also demonstrated that febantel was the drug responsible for removal of nematode parasites from dogs, while the other drug (praziquantel for tapeworm control) in Vercom Paste was shown to be without effect on nematodes and without any effect on the action of febantel. The febantel dosage, route of administration (oral) and proposed nematode label claims for Rintal Tabs are identical to the nematode claims approved for Vercom Paste. Therefore, the nematode effectiveness data for Vercom Paste (NADA 133-953, 50 FR 19167, May 7, 1985 and 53 FR 48532, December 1, 1988) as described in the Vercom Paste F.O.I. Summaries are summarized for reference beginning on page 7.

a. Pivotal Studies - Rintal Tabs

Rintal Tabs Anthelmintic Tablets were formulated to provide the same dosage of febantel as provided by Vercom Paste in the trials summarized below. Bioequivalence studies were conducted against representative nematode parasites in the canine and feline species to demonstrate that febantel given in tablet form for removal of nematodes is bioequivalent to febantel given in paste form as the approved product, Vercom Paste. A limited clinical trial was also conducted with Rintal Tabs (febantel tablets) to provide additional information.

Bioequivalence Studies

Three well controlled bioequivalence studies were conducted according to the Center for Veterinary Medicine's (CVM's) *Guideline for Efficacy Evaluation of Canine/Feline Anthelmintics* and *Bioequivalence Guideline.* The three studies were conducted in puppies, cats and dogs. Each study involved 3 groups of 10 animals infected with intestinal nematode parasites. Pretreatment worm egg counts (worm eggs/g feces) were performed and animals were ranked according to that count. After ranking they were blocked in groups of 3 and randomly assigned to 1 of the 3 treatments using a separate computer generated randomization sheet for each study. In all 3 studies one group of animals was treated with the test product (the formulation of febantel tablets intended to be marketed), a second group received the positive control

reference drug (Vercom Paste) and the third (negative control) group received placebo tablets. Treatments were given orally daily for 3 days. The studies were blinded with respect to the identity of the tablets. Egg counts were again performed post-treatment and the animals were euthanatized 7 days after the first day of treatment. Worms remaining in the intestinal tract were collected, identified and counted. The percent reduction of the population of each parasite present was calculated to determine effectiveness.

1. Dr. T. J. Kennedy, AEF Research, Waunakee, WI

This well controlled study was conducted in puppies to demonstrate that febantel in tablet form (Rintal Tabs) is bioequivalent to febantel in paste form (Vercom Paste) for the removal of nematodes. The 30 puppies were fewer than 6 months of age and were shown by pretreatment worm eggs/g feces counts to be infected with nematode parasites. After assignment to treatment groups, each animal was treated orally on a full stomach for 3 consecutive days. Two groups were treated with 15 mg/kg febantel daily for 3 days (Rintal Tabs and Vercom Paste) and 1 group received placebo tablets. In addition to blinding the tablet identity, the parasitology laboratory personnel were not aware of which treatment individual animals received. No side effects were observed after treatment. Post-treatment worm egg counts were obtained and the puppies were euthanatized 7 days after the first day of treatment. The intestinal parasites present were collected, identified and counted, and the percent reduction of each parasite was calculated. The results are summarized in Table 1.

Table 1. Summary of bioequivalence Study in Puppies

	Rintal Tabs		Vercom Paste		Placebo*	
Nematode	No. Infect	% Effic.	No. Infect	% Effic.	No. Infect	% Effic.
Hookworms						
Ancylostoma caninum	10	99.8	10	98.6	10	--
Uncinaria stenocephala	6	100	6	100	6	--
Total infections	16		16		16	
Ascarids						
Toxocara canis	6	100	5	100	8	--
Toxascaris leonina	6	98.9	6	98.3	6	--
Total infections	12		11		14	

* In the placebo group the number infected was determined at necropsy.

Conclusions:

Rintal Tabs Anthelmintic Tablets are bioequivalent to febantel given as the approved drug, Vercom Paste.

2. Dr. T. A. Yazwinski, University of Arkansas, Fayetteville, AR

This well controlled study was conducted in adult cats (6 months or more of age) to demonstrate the bioequivalency of febantel tablets (Rintal Tabs) to febantel given in paste form (Vercom Paste) against intestinal nematodes. The 30 cats were infected with nematodes, as determined by pretreatment worm egg counts. Each animal was treated orally for 3 consecutive days after assignment to a treatment group. The investigator was not aware which tablet contained febantel. One group of cats received Rintal Tabs, 1 received Vercom Paste and 1 received placebo tablets. The febantel dosage was 10 mg/kg/day for 3 days, given both as Rintal Tabs and Vercom Paste. No side effects were observed after treatment. Post-treatment worm egg counts were obtained, and the cats were euthanatized 7 days after the first day of treatment. The nematodes present in the intestinal tract were collected, identified and counted. The percent efficacy against each parasite is given in Table 2.

Table 2. Summary of bioequivalence Study in Cats

	Rintal Tabs		Vercom Paste		Placebo*	
Nematode	No. Infect	% Effic.	No. Infect	% Effic.	No. Infect	% Effic.
Hookworms *Ancylostoma tubaeforme*	8	99.7	6	99.1	6	--
Ascarids *Toxocara cati*	10	99.7	6	95.1	6	--

* In the placebo group the number infected was determined at necropsy.

Conclusions: Rintal Tabs Anthelmintic Tablets are bioequivalent to febantel given as the approved drug, Vercom Paste.

3. Dr. E. C. Greiner, University of Florida, Gainesville, FL

This well-controlled bioequivalence study utilized mature (6 months old or older) dogs to show that febantel given as Rintal Tabs is bioequivalent to febantel given as Vercom Paste against hookworms (*Ancylostoma canium* and *Ancylostoma braziliense*)and whipworms (*Trichuris vulpis*). The 30 dogs were shown by pretreatment worm egg counts to harbor infections of common intestinal nematodes and were assigned in groups of 10 to 3 different treatments. The treatments were given orally for 3 days to dogs in each of the 3 treatment groups. One group received Rintal Tabs at a febantel rate of 10 mg/kg daily, while a second group received 10 mg/kg febantel provided as Vercom Paste (positive control reference drug). The third group received placebo tablets. No side effects occurred after treatment. Post-treatment fecal samples were collected for worm egg counts, and the dogs were euthanatized 7 days after the first daily treatment. The intestinal nematodes present were collected, identified and counted. The percent efficacy of Rintal Tabs and Vercom Paste against the nematode parasites was calculated and is listed in Table 3.

Table 3. Summary of bioequivalence Study in Dogs

	Rintal Tabs		Vercom Paste		Placebo*	
Nematode	No. Infect	% Effic.	No. Infect	% Effic.	No. Infect	% Effic.
Hookworms *Ancylostoma sp. (A. caninum+ A. braziliense)*	10	98.3	10	99.7	10	--
Whipworms *Trichuris vulpis*	10	99.7	9	96.4	8	--

* In the placebo group the number infected was determined at necropsy.

Conclusions: Rintal Tabs Anthelmintic Tablets are effective against nematodes of dogs and are bioequivalent to febantel given as the approved reference drug, Vercom Paste.

b. Pivotal Studies - Vercom Paste F.O.I. Efficacy Data Summary

1. Dr. M. L Sharp, Vernon, TX conducted a well-controlled final oral dose titration study in dogs that included groups treated with febantel alone, praziquantel alone and the two compounds in combination (Vercom Paste). The febantel dosage used alone and in Vercom Paste (10 mg/kg/day, 3 days) was identical to that given as Rintal Tabs (febantel tablets) in the bioequivalence studies and the clinical trial discussed above under 4a. Pivotal Studies - Rintal Tabs. Five dogs were treated, with febantel alone, with 100% efficacy obtained against hookworms (ancylostoma caninum), ascarids (Toxocara canis) and whipworms (Trichuris vulpis). When praziquantel alone was given to 5 dogs at 1 mg/kg/day for 3 days, efficacy against A. caninum, T. canis and T. vulpis was essentially zero (0-2.4%), demonstrating that praziquantel was not effective against nematodes controlled by febantel. When the compounds were combined as Vercom Paste and given to 30 dogs daily for 3 days at a dosage of 10 mg febantel + 1 mg praziquantel/kg/day, efficacy against hookworms, ascarids, whipworms and tapeworms was 99.5-100%. This demonstrated that the nematode control by febantel was not changed by the presence of praziquantel.
2. Additional well-controlled oral dose confirmation studies in dogs with Vercom Paste (10 mg febantel + 1 mg praziquantel kg/day, 3 days) were conducted by Dr. R. M. Corwin, Columbia, MO (12 animals) and by Drs. R. G. Arther and D. D. Cox, Shawnee, KS (30 animals). Efficacy against hookworms (A. caninum), ascarids (T. canis) and whipworms (T. vulpis) was 99.9-100% in Dr. Corwin's study. In the study by Drs. Arther and Cox, efficacy was 97.3-100% against hookworms (A. caninum, Uncinaria stenocephala), 85.1% and 94.3% against T. canis and Toxascaris leonina, and 100% against T. vulpis.
3. Dr. E. L. Roberson, Athens, GA conducted a well-controlled study in cats, in which febantel and praziquantel were given orally alone and in combination. When four animals were treated with 10 mg febantel/kg/day for 3 days (the dosage used in the Rintal Tabs studies), efficacy was 93.3% against hookworms (Ancylostoma tubaeforme) and 98.8% against ascarids (Toxocara cati). Praziquantel alone at 1 mg/kg/day for 3 days was ineffective (0-39.2%) against these nematode parasites in 5 animals. When febantel and praziquantel were

used together (Vercom Paste) in 11 animals, efficacy was 95.1-100% against hookworms, ascarids and tapeworms. As in Dr. Sharp's study (see b.1 above), this trial demonstrated that febantel is effective against nematodes while praziquantel is not, and the efficacy of febantel was unchanged by the presence of praziquantel.

4. Other well-controlled studies in cats included a dose titration study by Drs. R. G. Arther and D. D. Cox, Shawnee, KS and a dose confirmation study by Dr. R. M. Corwin, Columbia MO. The oral dosage of 10 mg febantel/kg/day (same febantel dosage as provided by Rintal Tabs) plus 1 mg praziquantel/kg/day for 3 days resulted in 92.1-100% removal of hookworms (A. tubaeforme) and ascarids (T. cati, T. leonina) in 28 cats treated by Drs. Arther and Cox. Efficacy was 100% against hookworms and ascarids in 11 cats treated by Dr. Corwin.
5. A well-controlled dose titration study was conducted with puppies and well-controlled dose confirmation studies were done with puppies and kittens less than 6 months of age. The approved oral puppy and kitten dosage for febantel + praziquantel (Vercom Paste) is 15 mg febantel plus 1.5 mg praziquantel/kg/day for 3 days dosed on a full stomach, which is the same dosage of febantel as was evaluated in puppies and kittens in the Rintal Tabs (febantel tablets) studies. Dr. E. L. Roberson, Athens, GA treated 10 puppies with 15 mg/febantel + 1.5 mg praziquantel/kg/day for 3 days on a full stomach and obtained 91.3-97.9% control of hookworms (A. caninum) and ascarids (T. canis). Dr. M. L. Sharp, Vernon, TX treated 22 puppies on a full stomach at the same dosage as Dr. Roberson and obtained 99.3-99.8% efficacy against hookworms and ascarids. Kittens less than 6 months of age were treated orally on a full stomach with 15 mg febantel + 1.5 mg praziquantel/day for 3 days in well-controlled trials by Dr. E. L. Roberson, Athens, GA and Drs. R. G. Arther and D. D. Cox, Shawnee, KS. In Dr. Roberson's study with 12 kittens, efficacy was 95.9-100% for hookworms (A. tubaeforme) and ascarids (T. cati). Efficacy in 13 animals treated by Drs. Arther and Cox was 94.3-94.5% for hookworms and ascarids.
6. In the Vercom Paste (febantel + praziquantel) clinical trials 22 investigators from 15 geographical locations participated in the clinical evaluation of Vercom Paste in dogs, cats, puppies and kittens. The investigators treated 514 canines. The efficacy, based on fecal samples being free of the parasite eggs after treatment, was 97.6-100% for hookworms (Ancylostoma sp.), 100% for ascarids (Toxocara sp.) and 99.2 - 100% for whipworms (T. vulpis). Efficacy in 125 felines was 90.9-100% against hookworms and ascarids.
7. A supplemental application to the original Vercom NADA provided for additional claims in dogs and puppies for removal of hookworms (*Uncinaria stenocephala*) and ascarids (*Toxascaris leonina(* (NADA 133-953, 53 FR 48532, December 1, 1988). The supplemental F.O.I. Summary includes data from the original F.O.I. Summary for two controlled studies by Drs. R. Arther and D. Cox, Shawnee, KS, and additional data from a study by Dr. T. Kennedy, Waunakee, WI. Efficacy in these 3 studies was 99.5-100% against *U. stenocephala* in 20 animals and 91.8-100% against *T. leonina* in 18 animals. The original Vercom Paste clinical trial data showed that 98% of infected animals were cleared of hookworms (*U. stenocephala*) and 100% were cleared of ascarids (T. leonina).

c. Corroborative Study *Rintal Tabs (Febantel Tablets) Clinical Field Trial*

A clinical trial to supplement data obtained in the bioequivalence studies was conducted by six investigators using the same protocol. The investigators are listed below:

Dr. R. L. Blake, Oklahoma City, OK
Dr. J. B. Dalley, East Lansing, MI
Dr. K. G. Huggins, Lenexa, KS
Dr. T. M. Lamp, Bellville, TX
Dr. J. A. Nelson, Manhattan, KS
Dr. J. H. Sameck, Gainesville, FL

The purpose of the clinical trial was to confirm the effectiveness of febantel tablets (Rintal Tabs) for treatment of naturally occurring infections of intestinal nematodes of dogs, cats, puppies and kittens. Effectiveness was determined by obtaining pretreatment and post-treatment nematode egg counts and calculating the percent reduction after treatment. Each animal served as its own control. Post-treatment counts were made 7-10 days after the first day of treatment. Two sizes of the formulation of febantel to be marketed (Rintal Tabs Anthelmintic Tablets; 27.2 mg and 163.3 mg) were used. The oral dosages of febantel used daily for 3 days were 10 mg/kg body weight/day for dogs and cats; 15 mg/kg/day on a full stomach for puppies and kittens fewer than 6 months of age.

The six investigators treated 129 animals with Rintal Tabs. The evaluation of effectiveness was based on 117 fully completed cases (25 dogs, 28 cats, 23 puppies, 41 kittens). Twelve cases were excluded from effectiveness evaluation because of protocol deviations; i.e., not returned for post-treatment evaluation or post-treatment egg counts were not obtained, evaluation not done at proper time, or incorrect dosage was administered.

The nematode eggs present in pretreatment and post-treatment fecal samples were identified and counted. The number of animals treated and the percent egg count reduction for each parasite in dogs, cats, puppies and kittens in the clinical trial are given in Table 4.

Table 4. Clinical Trial Efficacy of Rintal Tabs (Febantel Tablets) Against Nematodes in Dogs, Cats, Puppies and Kittens

Parasite	No. Animals Treated*	Percent Egg Count Reduction
Dogs		
Hookworms *Ancylostoma*	21	100
Ascarids		
Toxocara	1	100
Toxascaris	1	100
Whipworms *Trichuris*	17	100
Cats		
Hookworm *Ancylostoma*	19	100
Ascarids *Toxocara*	12	98.7
Puppies		
Hookworms *Ancylostoma*	22	99.9
Ascarids		
Toxocara	9	100
Toxascaris	2	100
Whipworms *Trichuris*	6	100
Kittens		
Hookworm *Ancylostoma*	1	100
Ascarids *Toxocara*	39	99.6

* Some animals were infested with multiple parasite species.

The percent reduction shown above was calculated as follows: Pretreatment egg count - Post-treatment egg count / Pretreatment egg count X 100

Conclusion: Rintal Tabs were effective against all nematode parasites in dogs, cats, puppies and kittens. The small number of kittens infested with *Ancylostoma tubaeforme* is acceptable/adequate because of the data accumulated on the use and effectiveness of the drug on *Ancylostoma s.p.p.* in canines and felines of various ages.

Overall Rintal Tabs (Febantel Tablets) Clinical Trial Summary

The average percent reduction of hookworm, ascarid and whipworm egg counts ranged from 99.6 to 100% (Table 4). The average reduction of nematode (hookworm, ascarid, whipworm) egg counts for all parasites (all cases, all investigators) was as follows: dogs (100%), cats (99.7%), puppies (99.9%) and kittens (99.6%). The results of this clinical trial thus confirmed the results of the 3 bioequivalence studies. The recommended treatment of Rintal Tabs Anthelmintic Tablets was found to be effective under the conditions of the clinical trial.

III. TARGET ANIMAL SAFETY

a. Pivotal Preclinical Studies (Dogs)

Two preclinical safety studies were conducted in dogs with the febantel tablet formulation in accordance with FDA's Good Laboratory Practice regulations.

1. Drug Tolerance Test (Drug Tolerance Test for the Use of Febantel Tablets in Dogs)

M. Kohlenberg of Shawnee Mission, Kansas, conducted a drug tolerance evaluation in 3 dogs with the 163.3 mg tablet. One dog served as the nontreated control. A second dog received a daily treatment of 275 mg/kg for 9 consecutive days (12.5 times the proposed highest daily dose of 22 mg/kg for 3 times the proposed duration of 3 days). The third dog received a treatment of 550 mg/kg/day for 9 days (25 times the highest dose for 3 times the proposed labeled duration). Parameters monitored were clinical signs, body weights, clinical chemistries, hematology, necropsy and histopathology. The study was blinded in that the laboratory conducting the clinical chemistry/hematology evaluations was not advised of the treatments. Also, the individual conducting histological readings did not know which treatments were given. Table 5 presents a summary. The animal receiving the 275 mg/kg treatments had a slight weight loss, transient loss of appetite, some vomition/diarrhea, decreased WBC and decreased neutrophil count. No significant lesions were observed at necropsy or histologically. The dog which received the daily 550 mg/kg treatments showed significant weight loss, loss of appetite, vomition/diarrhea, depression, dehydration and slight incoordination. Elevated serum chemistry values included BUN and alkaline phosphatase while hematology parameters that decreased were the WBC, neutrophil and platelet counts. At necropsy, this animal had slight to marked redness of the gastrointestinal tract; microscopically, a few dilated crypts in the large intestine that were filled with cellular debris were observed. This finding was classified as possibly treatment-related. This study describes the toxic syndrome associated with massive overdoses of febantel tablets for a prolonged duration to dogs. The syndrome consists of induced clinical signs of toxicosis and altered clinical chemistry/hematology values.

Table 5. Drug Tolerance Test (Dogs)

Number of Animals	Treatment Rate	Results
1	Control	No clinical signs
1	275 mg/kg for 9 Days (12.5X highest anticipated use rate for 3X duration)	Vomition, diarrhea and inappetence
1	550 mg/kg for 9 Days (25X highest use rate for 3X duration)	Vomition, diarrhea, inappetence, depression and slight incoordination

2. General Safety Evaluation (General Safety Evaluation for the Use of Febantel Tablets in Dogs)

M. Kohlenberg also conducted a general safety study in 16 dogs using the 163.3 mg tablet. Four dogs, Group I, served as nontreated controls. Four dogs, Group II, received 22 mg of febantel/kg of body weight (the highest proposed daily dosage rate) for 9 consecutive days (3 times the proposed duration of treatment). The 4 dogs

in Groups III and IV received 66 and 110 mg/kg/day, respectively, for 9 days (9 and 15 times the highest proposed daily dosage rate, respectively, for 3 times the proposed duration of treatment). Parameters monitored were clinical signs, body weights, clinical chemistries, hematology, necropsy and histopathology. The study was blinded in that the laboratory conducting the clinical chemistry/hematology analyses was not advised of the treatments. Also, the individual conducting histological readings did not know which treatments were given. Table 6 presents a summary. No clinically significant signs or body weight changes were observed in the Group I, II or III dogs. Two dogs in Group IV also remained clinically normal throughout the study. The remaining 2 dogs receiving the 110 mg/kg daily treatments (Group IV) began showing clinical signs of inappetence, depression, salivation, vomition and dehydration on days 7 and 8 of treatment. These dogs expired on days 14 and 15 with additional hemorrhagic signs. No significant trends developed in the serum chemistry or hematology parameters for the Group I, II or III animals nor in 2 dogs within Group IV. The 2 dogs from Group IV which showed clinical signs also had some deviations from normal at the posttreatment sampling intervals. One had a lowered WBC (on day 8) with the other having lower WBC and platelet count and elevated bilirubin/CPK values (on day 15). No significant gross lesions were observed at necropsy except in the 2 animals from Group IV which expired. Their most prominent gross lesion was one of generalized redness in the major body systems. Histologically, all tissues from all study dogs were within normal limits.

Conclusion: No adverse effects were observed in dogs treated with this febantel formulation at a daily dose of 66 mg/kg for 9 consecutive days (3 times the proposed dose for 3 times the proposed duration of treatment).

Table 6. General Safety-Evaluation (Dogs)

Number of Animals	Treatment Rate	Results
4	Control	No clinically significant observations in any parameters in first three groups
4	22 mg/kg for 9 Days (Highest anticipated use rate for 3X duration)	
4	66 mg/kg for 9 Days (3X highest use rate for 3X duration)	
4	110 mg/kg for 9 Days (5X highest use rate for 3X duration)	Clinical signs of vomition, inappetence, depression, salivation, and death in 2 of 4.

b. Pivotal Preclinical Studies (Cats)

Three preclinical safety studies were conducted in cats with the febantel tablet formulation in accordance with FDA's Good Laboratory Practice regulations.

1. Drug Tolerance Test (Drug Tolerance Test for the Use of Febantel Tablets in Cats)

M. Kohlenberg conducted a drug tolerance evaluation in 3 cats to identify the toxic syndrome induced by an overdose of febantel tablets. The 27.2 mg tablets were

administered orally at the rate of 220 or 440 mg of febantel/kg of body weight for up to 9 consecutive days (10 to 20 times the highest proposed dose for 3 times the proposed duration of treatment). One cat served as the nontreated control. Parameters monitored were clinical signs, body weights, clinical chemistries, hematology, necropsy and histopathology. The study was blinded in that the laboratory evaluating the clinical chemistry/hematology parameters was not advised of the treatments. Also, the individual conducting histological readings did not know which treatments were given. Table 7 presents a summary. Treatments induced vomition, salivation, loss of appetite and diarrhea in both the 220 and 440 mg/kg treated cats. The cat receiving 440 mg/kg also showed depression and expired on day 9. A body weight loss was recorded for the cat receiving 220 mg/kg. No consistent trends developed in the clinical chemistry and hematology parameters which were evaluated at 3 and 10 days post-treatment, although elevations in CPK, SGOT and SGPT occurred. No clinically significant gross pathology was observed at the time of necropsy. There was no microscopic evidence of serious drug induced lesions. The findings of this study indicate that 440 mg of febantel/kg of body weight/day will induce death in cats when administered for 8 days. It further characterized the clinical signs of toxicosis preceding death (vomition, diarrhea, salivation, inappetence and depression).

Table 7. Drug Tolerance Test (Cats)

Number of Animals	Treatment Rate	Results
1	Control	No clinical signs
1	220 mg/kg for 9 Days (10X highest anticipated use rate for 3X duration)	Clincal signs of vomition, diarrhea, salivation and loss of appetite in both treated animals and death at 440 mg/kg
1	440 mg/kg for 9 Days (20X highest use rate for 3X duration)	

2. General Safety Evaluation (General Safety Evaluation for the Use of Febantel Tablets in Cats)

M. Kohlenberg also conducted a general safety study in 16 adult male and female cats which were orally dosed with 27.2 mg febantel tablets for 9 consecutive days (3 times the proposed duration of treatment). Four cats served as nontreated controls (Group I). Groups II, III and IV received 22 (maximum proposed use rate), 66 or 110 mg of active ingredient/kg of body weight, respectively. Parameters monitored were clinical signs, body weights, clinical chemistries, hematology, necropsy and histopathology. The study was blinded in that the laboratory conducting the clinical chemistry/hematology analyses was not advised of the treatments. Also, the individual conducting histological readings did not know which treatments were given. Table 8 presents a summary. No significant clinical signs were observed in the Group I and Group II cats. One of 4 cats in Group III had signs progressing to severe depression/ dehydration and was euthanatized for humane reasons. Two of the 4 animals in Group IV expired during the study. Pretreatment clinical chemistry and hematology values revealed numerous abnormalities indicative of liver and kidney dysfunction as well as infectious conditions. No dose related trends occurred for these parameters in the cats not showing clinical signs. Necropsy observations showed liver, kidney or lung lesions for the 3 cats which did not complete the study. Histology

confirmed the presence of chronic liver cirrhosis in 2 cats and chronic nephritis lesions for 2 animals. The 3 cats which expired or were euthanatized were included in the group of 4 that were microscopically diagnosed as having those chronic pre-existing conditions. No adverse effects were observed following treatment of adult, random source cats with febantel tablets at a daily rate of 22 mg/kg for 9 consecutive days. It was recommended that a further study be conducted in cats which are without the complications of chronic renal or liver pathology.

Table 8. General Safety-Evaluation (Cats)

Number of Animals	**Treatment Rate Control**	**Results**
4	Control	No clinically significant signs in the first two groups
4	22 mg/kg for 9 Days (Highest anticipated use rate for 3X duration)	
4	66 mg/kg for 9 Days (3X highest use rate for 3X duration)	Clinical signs of vomition, slight loss of appetite.
4	110 mg/kg for 9 Days (5X highest use rate for 3X duration)	Complications of pre-existing liver and kidney dysfunction. Two of 4 receiving 110 mg/kg expired.

3. General Safety Evaluation (Additional General Safety Evaluation for the Use of Febantel Tablets in Cats)

M. Kohlenberg conducted an additional general safety study in 16 cats. They were orally dosed with 27.2 mg febantel tablets for 9 consecutive days (3 times the recommended duration of treatment). Four cats served as nontreated controls (Group I). Groups II, III and IV received 22 (maximum proposed use rate), 66 or 110 mg of active ingredient/kg of body weight, respectively. Parameters monitored were clinical signs, body weights, clinical chemistries, hematology, necropsy and histopathology. The study was blinded in that the laboratory personnel conducting the clinical chemistry/hematology evaluations were not advised of the treatments. Also, the individual conducting histological readings did not know which treatments were given. Table 9 presents a summary. No significant clinical signs were observed in any of the 16 cats, during the study. Body weights remained stable during the study. No clinically significant trends developed in the group means for the clinical chemistry or hematology parameters. Lesions observed at necropsy did not appear to be treatment-related. The histology report indicated no significant histopathologic changes in any of the cats that would be attributed to treatment with febantel tablets. *Conclusion:* Safety for the oral treatment of cats with a 27.2 mg tablet formulation of febantel is demonstrated at dosages up to and including 110 mg of active ingredient per kg of body weight for 9 consecutive days (5 times the maximum proposed dose for 3 times the proposed duration of treatment).

Table 9. Additional General Safety Evaluation (Cats)

Number of Animals	Treatment Rate	Results
4	Control	No effects occurred upon any parameters in any of the 4 groups
4	22 mg/kg for 9 Days (Highest anticipated use rate for 3X duration)	
4	66 mg/kg for 9 Days (3X highest use rate for 3X duration)	
4	110 mg/kg for 9 Days (5X highest use rate for 3X duration)	

Due to the association of deaths in cats with pre-existing liver and/or kidney dysfunction treated at elevated doses with Rintal Tabs, the label and package inserts contain the following statement: *Warning:* Consider alternative therapy or use with caution in animalswith pre-existing liver or kidney dysfunction. See *Animal Toxicology*section for additional information.

c. Pivotal Studies - Vercom Paste F.O.I. Safety Data Summary

1. Reference is also made to Vercom Paste NADA 133-953 (febantel and praziquantel) which contains 13 preclinical safety evaluations in dogs conducted in accordance with FDA's Good Laboratory Practice regulations. Six of the studies were conducted with a febantel paste formulation and 7 were completed with a combination febantel and praziquantel paste formulation.
2. Reference is again made to NADA 133-953 which contains 2 preclinical safety studies in cats conducted with a febantel paste formulation and 5 evaluations with a combination febantel and praziquantel paste formulation. The studies were conducted in accordance with FDA's Good Laboratory Practice regulations.
3. Preclinical safety studies in NADA 133-953 are also referenced as the basis for the following statement on the package insert:

"CONTRAINDICATIONS: DO NOT USE IN PREGNANT ANIMALS. Elevated treatments (6 consecutive days with 3 times the labeled dosage rate) with febantel to dogs and cats in early pregnancy induced an increased incidence of abortion and fetal abnormalities."

d. Corroborative Study

Clinical Field Trial (Dogs and Cats)

The six investigators treated 129 animals with Rintal Tabs. The safety evaluation was based on 126 cases that were treated and evaluated for safety. Three cases were not included in the safety evaluation because the animals were not returned for posttreatment evaluation. Confirmation of safety for the use of 27.2 and 163.3 mg Rintal Tabs (febantel) Anthelmintic Tablets was achieved in clinical field trials by veterinary practitioners located in various geographical areas of the United States. A total of 26 dogs (greater than 6 months of age), 30 puppies (fewer than 6 months of age), 28 cats (greater than 6 months of age) and 42 kittens (fewer than 6 months of age) were treated for 3 consecutive days with the label dosage schedule. All animals

treated and evaluated post-treatment were included in this safety evaluation despite not all being included in the effectiveness evaluation. Breeds of dogs and cats were representative of the United States canine and feline population with no breed susceptibility observed. Weight range for the treated animals was one to 86.6 lb. Body weight was not a factor for potential hazard. Age of the animals was again representative with a range of one month to 10 years. No age susceptibility was observed. Males and females were both represented with no difference in safety observed. No drug related side effects were observed. Veterinary practitioners conducting the clinical field trials rated overall safety as excellent for 93.7% of the cases and 6.3% as good. In conclusion, the clinical field trial safety evaluations substantiate an adequate safety margin for the treatment of dogs, puppies, cats and kittens as per the label instructions. Table 10 presents a summary.

Table 10. Safety in Clinical Field Trial (Dogs and Cats)

Number of Animals	Treatment Rate	Results
26 Dogs (> 6 months of age)	3 consecutive days with the label dosage schedule for all dogs, puppies, cats, and kittens	Veterinary Practitioners rated safety as excellent for 93.7% of the total cases (dogs, puppies, cats, and kittens) and 6.3% as good
30 Puppies (< 6 months of age)		
28 Cats (> 6 months of age)		
42 Kittens (< 6 months of age)		

IV. HUMAN FOOD SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug (febantel) formulation is labeled for use in dogs and cats only.

V. USER SAFETY

Laboratory animal toxicity studies verify the lack of potential hazards to human handling of the formulation. The label states: Keep out of reach of children.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of Section 512 of the act and Section 514.111 of the implementing regulations. Those data demonstrate that Rintal Tabs (febantel) are safe and effective for the labeled indications when used in accordance with the labeled directions for use. Under Section 512(c)(2)(F)(ii) of the Federal Food, Drug and Cosmetic Act, this NADA qualifies for a three year term of marketing exclusivity because this product is a new dosage form (tablet) requiring new clinical studies to demonstrate target animal safety.

For the safe and effective use of Rintal Tabs, it is necessary to diagnose the existence of nematode infestation and to avoid the treatment of those animals suffering from renal and/or hepatic disease. The expertise of a trained professional is required to diagnose these problems; therefore, the drug is a prescription product.

VII. LABELING (Attached)

Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.