Date of Approval: May 4, 2018

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-481

Mirataz™

mirtazapine transdermal ointment

Cats

For the management of weight loss in cats

Sponsored by:

Kindred Biosciences, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-481

B. Sponsor

Kindred Biosciences, Inc.
1555 Bayshore Highway, suite 200
Burlingame, CA 94010

Drug Labeler Code: 86078

C. Proprietary Name

Mirataz™

D. Product Established Name

Mirtazapine transdermal ointment

E. Pharmacological Category

α2-adrenergic receptor antagonist, nor-adrenergic and serotonergic drug

F. Dosage Form

Transdermal Ointment

G. Amount of Active Ingredient

Each 1 g of Mirataz™ contains 20 mg of mirtazapine (2%). Each 5 g tube contains 100 mg (0.1 g) of mirtazapine.

H. How Supplied

Supplied in individual 5-gram, multi-dose aluminum tubes packaged in a carton of one tube

I. Dispensing Status

Rx

J. Dosage Regimen

Administer topically by applying a 1.5-inch ribbon of ointment (approximately 2 mg/cat) on the inner pinna of the cat's ear once daily for 14 days.

K. Route of Administration

Topical (transdermal)

L. Species/Class

Cats

M. Indication

For the management of weight loss in cats

II. EFFECTIVENESS

The effectiveness of Mirataz™ was demonstrated in one adequate and well-controlled clinical field study described below (B. Substantial Evidence). Mirataz™ was administered to 115 client-owned cats. The most common adverse reactions were erythema at the application site, vocalization, hyperactivity, and vomiting (likely from grooming the ointment off the ears). This study demonstrated that Mirataz™ is effective at increasing the bodyweight in cats with a history of weight loss when administered at approximately 2 mg/cat every day for 14 days.

A. Dosage Characterization

The dosage characterization is based on published literature utilizing mirtazapine oral tablets in cats and multiple pilot studies using the topical ointment. The pilot studies, in collaboration with the literature, established a dose of approximately 0.1 g/cat of Mirataz™ (2 mg/cat of mirtazapine or approximately 0.5 mg/kg for an average 9-pound cat) applied daily as a 1.5-inch ribbon length of ointment to the pinna of the cat's ear. Therefore, the dose of approximately 0.1 g/cat of Mirataz™ (2 mg/cat of mirtazapine) was further evaluated in the clinical field study described in the Substantial Evidence section.

Results from published literature using generic oral (human) tablets in cats provided the basis for the initial dose (0.5-1.1 mg/kg) to be tested in pilot studies. Multi-dose topical application of six various test formulations to the inner pinna of the cat's ear at a dosage of 1.1 mg/kg resulted in a lower maximum concentration (Cmax) than seen with oral ingestion of generic oral tablets, but with a similar area under the concentration-curve (AUC) and a longer half-life. Because the Cmax may be related to adverse effects, the formulation selected for further development was chosen due to its similar AUC and lower Cmax compared to generic oral tablets.

An additional pilot study demonstrated that cats receiving dosages of 0.5 mg/kg and 1.1 mg/kg using non-final formulation 2% and 4% ointments had an increase in body weight gain and food intake at both dose levels compared to cats receiving vehicle ointment. There were no differences in effectiveness between the high- and low-dose groups and the drug formulation was tolerated at both dose levels. The lower dose formulation (2%; 0.5 mg/kg; approximately 2 mg per cat) was chosen due to similar results in effectiveness and safety.

A pharmacokinetic study comparing the oral and transdermal (pinna) bioavailability of 0.5 mg/kg ointment (final formulation) in cats wearing Elizabethan collars demonstrated that the oral bioavailability of the ointment can be up to two-fold higher than the transdermal bioavailability. A pilot effectiveness study conducted in cats wearing Elizabethan collars at a dose of 0.5 mg/kg and 2.1 mg/kg ointment (final formulation) administered topically (pinna) once a day

for 14 days supported the effectiveness of 0.5 mg/kg administered topically and provided steady state pharmacokinetic data.

Thirty-two client-owned cats were enrolled in a multicenter, randomized, owner-masked, vehicle-controlled pilot study to evaluate the use of the final market transdermal formulation of mirtazapine under field conditions for the management of weight loss in cats. Sixteen cats received mirtazapine transdermal ointment and 16 cats received a vehicle control. A dose of approximately 2 mg/cat/day was applied to the inner pinna of the ear once daily for 28 days (± 3 days). A ribbon of ointment (approximately 0.1 g) was placed onto the pinna of the cat's ear and spread over the inner (anterior) surface of the pinna using a gloved finger. Owners were provided dosing cards to assist in measuring the ointment ribbon length. In the mirtazapine group (dosed between approximately 0.3 – 0.8 mg/kg), the mean percent bodyweight change was an increase of 3.25% at Week 2 compared to baseline. In the control group, the mean percent weight change was a decrease of 1.65% at Week 2 compared to baseline. The mean body weights of both groups showed little change from Week 2 to Week 4. The most common adverse reactions were vomiting (5 cats in the mirtazapine group, 2 cats in the control group) and application site irritation (3 cats in the mirtazapine group, 2 cats in the control group). One cat in the mirtazapine group was reported with an adverse reaction of aggression. There were no serious adverse reactions reported in the mirtazapine group.

B. Substantial Evidence

1. Clinical Field Study

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Pivotal Field Effectiveness Study of Topical (Transdermal) Mirtazapine 2% Ointment for Management of Weight Loss in Cats. (Study No. KB105)

Study Dates: October 2015 to August 2016

Study Locations:

Orange, CA	Leawood, KS
Vista, CA	Baltimore, MD
Colorado Springs, CO	Kentwood, MI
Colorado Springs, CO	Waterford, MI
Bloomfield, CT	St. Louis, MO
Stamford, CT	South Euclid, OH
Lake Worth, FL	Tulsa, OK
Largo, FL	Quakertown, PA
Chicago, IL	Providence, RI
Decatur, IL	Alexandria, VA

Study Design:

Objective: The primary objective of this GCP study was to demonstrate the effectiveness and field safety of Mirataz™ (mirtazapine transdermal ointment) for the management of weight loss in cats under clinical conditions.

Study Animals: A total of 230 client-owned cats were enrolled and received Mirataz™ or vehicle control during the study. The age of the cats ranged from 2.8 to 24.6 years old, and the body weight ranged from 2.1 to 9.2 kg. The study included 106 neutered males, 123 spayed females, and 1 intact female and the most common breed was Domestic Shorthair (63.0%).

Cats were required to have existing documented medical history of ≥ 5% weight loss deemed clinically significant by the Investigator. The most common pre-existing conditions included renal insufficiency (42.6% of cats in the Mirataz™ group, 30.4% of cats in the vehicle control group), vomiting (27.8% of cats in the Mirataz™ group, 28.3% of cats in the vehicle control group), and hyperthyroidism (18.3% of cats in the Mirataz™ group, 13.0% of cats in the vehicle control group). Some cats had more than one pre-existing condition.

Experimental Design:

Treatment Groups:
Table II.1. Treatment Groups

Treatment Group	**Dose**	**Safety Evaluation # of cats**	**Effectiveness Evaluation # of cats**
Mirataz™	2 mg/cat	115	83
Vehicle Control	0 mg/cat	115	94

Randomization: Cats were randomized in a 1:1 ratio of Mirataz™ to vehicle control using centralized block randomization with a block size of 4. Treatment groups were identified by 4 treatment letter codes (A, B, C, D) with two letters corresponding to Mirataz™ and two letters corresponding to vehicle control. A randomization list was generated and uploaded to the electronic data capture system (EDC) by an independent, third party statistician.

Masking: Both the Mirataz™ and vehicle control had the same appearance and coloration, and were packaged identically. The two products were identical in every aspect, differing only in the presence of the active compound.

Study site personnel maintained masking by separation of function. Study site personnel completing randomization, dosing on Day 1, and drug accountability were exclusively responsible for handling the Mirataz™ and vehicle control, and dispensing study drug. These study site personnel had access to the treatment code assignment (A, B, C, D), but did not have the letter code assignment.

The Investigator was masked to both treatment code assignments and letter code assignments. Cat Owners remained masked to treatment group throughout the study.

Inclusion Criteria: Cats were required to be ≥ 1 year of age at day 1 of study start. All cats must have had existing documented medical history of ≥ 5% weight loss deemed clinically significant by the Investigator.

Exclusion Criteria: Cats were ineligible for study enrollment if they:

- Were pregnant or lactating
- Weighed less than 2.0 kg on Day 1
- Were expected to require intensive medical intervention during the study due to progression of underlying disease
- Could not reasonably be expected to survive the study
- Had diagnosed neoplasia
- Had severe renal failure (International Renal Interest Society [IRIS] grade > 3 or serum creatinine > 5.0 mg/dL)
- Had a change in food type within 7 days from Day 1
- Had received prohibited concomitant medication(s)
    - Mirtazapine within 30 days prior to Day 1
    - Other medications intended to stimulate appetite or weight gain in cats or expected to interfere with the treatment were not allowed for 7 days prior to Day 1, which included but were not limited to the following: diazepam, oxazepam, phenothiazines, metoclopramide, cyproheptadine, maropitant, and dronabinol
    - Monoamine oxidase inhibitors and serotonergic drugs within 14 days of Day 1

Concomitant Medications: Intravenous fluids, chemotherapy, and other medications intended to stimulate appetite or weight gain in cats or expected to interfere with the treatment were prohibited between Day 1 and Study Termination. Cats receiving diuretics, insulin, and/or angiotensin converting enzyme (ACE) inhibitors must have been on a stable regimen at Day 1. Subcutaneous fluid as supportive therapy was permitted during the study.

Drug Administration: Mirataz™ was administered at a dose of approximately 0.1 g (2 mg of mirtazapine) per cat, dosed as a 1.5-inch ribbon. The vehicle control was an ointment containing the same inert ingredients without mirtazapine and was administered at the same dose. A 1.5-inch ribbon of ointment, constituting of approximately 0.1 g, was administered topically to the inner pinna of the cat's ear. Owners were instructed to wear gloves and a dosing card was provided to the owner to assist in estimating the appropriate ribbon length. Dose administrations could be alternated between ears. If desired, the pinna of the cat's ear could be cleaned by wiping with a tissue or cloth immediately prior to the next dose. The duration of dosing was once daily for 14 ± 3 days. To demonstrate dose administration, a trained staff member at the site administered the first dose on Day 1 in the clinic in the presence of the owner. Owners were instructed to separate the treated cat from people and other household pets for approximately 2 hours following treatment administration.

Measurements and Observations: At the Screening Visit, carried out between Day -14 to Day 1, a complete physical examination; body weight measurement; clinical pathology (hematology, serum chemistry, urinalysis, and fecal analysis); and recording of medical history were performed. On Day 1, cats were evaluated for eligibility for enrollment into the study by review of the inclusion and exclusion criteria following a complete physical examination and body weight measurement. The Screening and Day 1 Visits could have been combined for cats that met all inclusion criteria and no exclusion criteria. Baseline (Day 1) body weights were measured prior to

administering the first dose of study drug. At the Week 2 Visit (14 ± 3 days), a complete physical examination, body weight measurement, clinical pathology (hematology, serum chemistry, and urinalysis), and recording of adverse events were performed and the cat was terminated from the study. Following Study Termination, site study staff contacted owners via phone, email, or an in-person visit 5 to 9 days after termination to complete a Post-Study Owner Follow-up to assess for any adverse events. The Owners maintained an Owner Diary which included the Owner Diary Dose Log and Owner Diary Observed Events from the first dose (Day 1) to Study Termination. Unscheduled Visits were performed if necessary.

Statistical Methods: The primary effectiveness variable was percent change in body weight from Day 1 to Week 2. Superiority of Mirataz™ over the vehicle control group was established by a statistically significant difference ($p<0.05$) between the mean percent change in body weight in the 2 groups and a higher mean in the Mirataz™ group compared to the vehicle control group. Treatment effect was tested using independent sample t-test, assuming equal variances between the two treatment groups. Additionally, the effectiveness of Mirataz™ was established if the percent change in body weight in the Mirataz™ group is greater than or equal to 0.

Results:

Effectiveness: Effectiveness was evaluated in 177 cats (83 cats in the Mirataz™ group and 94 cats in the vehicle control group).

The mean percent body weight increase at Week 2 from Day 1 was 3.94% in the Mirataz™ group, and 0.41% in the vehicle control group. A two-sample t-test resulted in a p-value of <0.0001. A 95% confidence interval on the mean percent change in body weight for the Mirataz™ group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0. See Table II.2 below.

Table II.2. Percent Change (%) in Body Weight from Day 1 to Week 2

Group	Mean	Standard Deviation	95% Confidence Interval	p-value*
Mirataz™	3.94	5.37	2.77, 5.11	N/A
Vehicle Control	0.41	3.33	-0.27, 1.09	N/A
Difference	3.53	4.40	2.22, 4.84	<0.0001

*p-value from two-sample t-test.

Physical Examination: Abnormal physical examination findings observed any time after the first dose of study drug that were reported as clinically significant were reported as adverse reactions (see below).

Clinical Pathology: At Week 2, blood urea nitrogen (BUN) values were significantly higher in the Mirataz™ group compared to the vehicle control group ($p<0.10$). The BUN in the Mirataz™ group was 43.60 mg/dL (reference range 16-37 mg/dL) compared to 36.05 mg/dL in the vehicle control group. There were no other clinically significant changes in clinical pathology values

(hematology, serum chemistry, and urinalysis) between groups during the study.

For individual cats, abnormal clinical pathology results collected after the first dose of study drug that were outside reference ranges and were reported as clinically significant were reported as adverse reactions (see below).

Post Study Owner Follow-Up: Post study, follow-up was done in 199 cats (103 in the Mirataz™ group and 96 in the vehicle control group). Following cessation of Mirataz™, four cats were reported with being less social or less restless, one cat was reported as more active, and one cat was reported with increased hissing and urinating out of box.

Adverse Reactions:

Field safety was evaluated in 230 cats (115 cats in the Mirataz™ group and 115 cats in the vehicle control group). The vehicle control was an ointment containing the same inert ingredients as Mirataz™ without mirtazapine. The most common adverse reactions included application site reactions, behavioral abnormalities (vocalization and hyperactivity), and vomiting. The adverse reactions and number of cats experiencing each adverse reaction are summarized in Table II.3 below.

Table II.3. Adverse Reactions Reported During the Field Study

Adverse Reaction	**Mirataz™ N=115(%)**	**Vehicle Control N=115(%)**
Application site (Ear pinna)		
Erythema	12 (10.4%)	20 (17.4%)
Crust/Scab	3 (2.6%)	6 (5.2%)
Residue	3 (2.6%)	8 (7.0%)
Scaling/Dryness	3 (2.6%)	3 (2.6%)
Dermatitis or irritation	1 (0.9%)	9 (7.8%)
Alopecia	1 (0.9%)	2 (1.7%)
Pruritus	1 (0.9%)	4 (3.5%)
Behavioral		
Vocalization (including crying, mewing)	13 (11.3%)	2 (1.7%)
Hyperactivity (including pacing, restlessness, sleeplessness)	8 (7.0%)	1 (0.9%)
Disoriented state or ataxia	4 (3.5%)	2 (1.7%)
Lethargy (including depressed, sedation, weakness)	4 (3.5%)	9 (7.8%)
Attention Seeking	3 (2.6%)	0
Aggression	2 (1.7%)	0
Physical Examination or Observational		
Vomiting	13 (11.3%)	15 (13.0%)
Dehydration	6 (5.2%)	5 (4.3%)
Diarrhea or soft stool	6 (5.2%)	7 (6.1%)
Heart murmur	5 (4.3%)	7 (6.1%)

Adverse Reaction	Mirataz™ N=115(%)	Vehicle Control N=115(%)
Inappetence	5 (4.3%)	5 (4.3%)
Renal insufficiency*	4 (3.5%)	0
Ear infection	3 (2.6%)	0
Urinary tract infection	3 (2.6%)	0
Clinical Pathology		
Hematuria	7 (6.1%)	1 (0.9%)
Elevated BUN (without creatinine)**	6 (5.2%)	0
Elevated creatinine and BUN	5 (4.3%)	1 (0.9%)
Hyperphosphatemia	5 (4.3%)	0
Hypokalemia	5 (4.3%)	2 (1.7%)
Pyuria	5 (4.3%)	0
Anemia	3 (2.6%)	8 (7.0%)
Low urine specific gravity	3 (2.6%)	1 (0.9%)
Monocytosis	3 (2.6%)	2 (1.7%)
Neutrophilia	3 (2.6%)	2 (1.7%)

* One cat with renal insufficiency was reported with a serious adverse reaction of acute renal failure, hematuria, and pyuria at the Week 2 visit. The cat was enrolled with a history of chronic kidney disease. Euthanasia was elected, and necropsy revealed hypertrophic cardiomyopathy, bilateral parathyroid hyperplasia, and mild to moderate renal disease. The relationship to the drug is unknown due to the cat's concurrent disease.
** At Week 2, blood urea nitrogen (BUN) values were significantly higher in the Mirataz™ group compared to the vehicle control group ($p<0.10$). The BUN in the Mirataz™ group was 43.60 mg/dL (reference range 16-37 mg/dL) compared to 36.05 mg/dL in the vehicle control group.

Conclusions:

The topical administration of Mirataz™ to the inner pinna of the ear at a dose of 2 mg/cat for 14 days was effective and considered safe for the management of weight loss in cats.

III. TARGET ANIMAL SAFETY

The safety of Mirataz™ was demonstrated in one six-week laboratory margin of safety study and seven pilot studies described below. The purpose of these studies was to provide information on the safety of Mirataz™ when used according to the label in cats. The laboratory study was not randomized; therefore, bias may have been introduced. For this reason, additional safety information from seven pilot studies was used to support the safety of Mirataz™. The findings in all seven studies were consistent with the clinical field study and the six-week laboratory margin of safety study and support the safe use of mirtazapine when administered transdermally on the pinna at 2 mg/cat for 14 days in cats. Observations related to the test article and vehicle control include dose site reactions and effects on the urinary system. Observations related to the test article include increased vocalization, soliciting attention, hyperactivity/frantic behaviors, tremors, increased alanine aminotransferase (ALT) liver values, polyuria, polydipsia, hypersalivation,

isosthenuria, frank blood in the stool, and diarrhea. Oral administration resulted in excessive salivation and lip licking in most cats immediately following administration. These safety studies, in combination with the safety information collected in the clinical field study, demonstrate the safety of Mirataz™ when used according to the label.

A. Six-Week Laboratory Margin of Safety Study:

Title: A 6 Week Target Animal Safety Study of Topical (Transdermal) Mirtazapine in Cats. (Study No. KB115T)

Study Dates: December 2015 to September 2016

Study Location: Stouffville, ON, CANADA

Study Design:

Objective: The objective of this GLP study was to evaluate the safety of Mirataz™ (mirtazapine transdermal ointment) when administered topically to the inner pinna of the cats' ears once daily for 42 days at 0 mg/kg (vehicle control), 1.1 mg/kg, 3.2 mg/kg, and 5.3 mg/kg of body weight.

Study Animals: Forty-eight, intact, 7-10 month old purpose-bred domestic shorthaired cats, ranging in weight from 2.6-5.0 kg (5.7-11 lbs) at study initiation were sequentially assigned to four groups within gender. The vehicle control and 5.3 mg/kg groups consisted of eight males and eight females, while the 1.1 and 3.2 mg/kg groups consisted of four males and four females.

Experimental Design: Cats were blocked by gender. On Day -1, cats were ranked within study population by study animal ID number in ascending order and sequentially assigned to one of four groups within gender. Within dose groups and gender, cats were sequentially assigned by animal ID number to one of two cohorts, for study procedures and post-mortems. Study activities for cohort 2 cats followed those of cohort 1 cats by one day beginning on Day 0. Data continued to be collected from eight vehicle control (four male, four female) and eight 5.3 mg/kg (four male, four female) cats during a four-week recovery period prior to euthanasia and necropsy. Cats were sequentially assigned to early termination or recovery group and randomly assigned to cages. Animals were necropsied within cohort in cage number order. Any personnel collecting or recording data, including necropsy personnel, were masked to treatment. Personnel administering treatment were not masked. Personnel administering treatment were not involved in the assessments or collection of data.

Drug Administration: Four dose groups were included in this study. Cats received either a vehicle control or Mirataz™ at 1.1 mg/kg, 3.2 mg/kg, or 5.3 mg/kg. The vehicle control was an ointment containing the same inert ingredients without mirtazapine and was administered at the same volume amount as the 5.3 mg/kg dose group. The dose was applied topically to the inner pinna of the ear once daily for 42 days. The dose was adjusted per body weight on Days -1, 14, and 28. Initially the dose was applied to the right ear for the 1.1 and 3.2 mg/kg groups and was split between both ears for the vehicle control and 5.3 mg/kg groups from Day 0 to Day 10. Due to the development of redness, skin flaking, and

irritation to one or both ears associated with dosing, the protocol was amended to allow alternate ear dosing beginning on Day 11. Dose application for the vehicle control and 5.3 mg/kg groups was split between two dose rounds applied to the same ear with at least 15 minutes between rounds 1 and 2 for each cat. Dose application for the 1.1 and 3.2 mg/kg dose groups was completed in a single round.

Table III.1. Treatment Groups and Drug Administration

Group	No. Cats	Test Article	Dose (mg/kg)	Dose Route	Dose Frequency	Post-Mortem
T0	8 M 8 F	Vehicle Ointment	0	Topical (inner surface of pinna)	Daily for 42 days	Day 42/43 (4M, 4F); Day 70/71 (4M, 4F)
T1	4 M 4 F	Mirtazapine (2%) Ointment	1.1	Topical (inner surface of pinna)	Daily for 42 days	Day 42/43
T3	4 M 4 F	Mirtazapine (2%) Ointment	3.2	Topical (inner surface of pinna)	Daily for 42 days	Day 42/43
T5	8 M 8 F	Mirtazapine (2%) Ointment	5.3	Topical (inner surface of pinna)	Daily for 42 days	Day 42/43 (4M, 4F); Day 70/71 (4M, 4F)

Measurements and Observations: Viability observations were conducted twice daily (at least 6 hours apart). Clinical observations (including behavior and immediate post-dosing observations) were performed once daily. Physical examinations were performed twice during acclimation, biweekly during the dosing period, and once for cats in the recovery group prior to study termination. Body weights were measured twice during acclimation then weekly during the dosing and recovery periods. Food consumption was measured daily. Blood and urine were collected for clinical pathology (hematology, clinical chemistry, coagulation, urinalysis) twice during acclimation then approximately biweekly (i.e., three times) during the dosing period and once during the recovery period. Blood was collected for pharmacokinetics on Days 0 and 35 prior to dosing and at 1, 2, 4, 6, 8, 12, and 24 hours post-dosing. Single blood samples for pharmacokinetics were also collected prior to dosing on Days 7, 14, 21, and 28, and Days 56 and 69 for recovery cats. Ophthalmic examinations were conducted once during acclimation, once during the dosing period, and once during the recovery period. Electrocardiography was performed once during acclimation, twice during the dosing period, and once during the recovery period prior to study termination. Blood pressure was performed at baseline and then on Days 20, 35, 41, and 69 for Cohort 1 and Days 21 or 23, 35, 42, 69, and 70 for Cohort 2. All cats were

euthanized and underwent full gross necropsy either on Day 42/ 43, or 4 weeks later for the recovery group cats.

Statistical Methods:

For continuous variables, summary statistics (mean, standard deviation, minimum, maximum, and number of animals) for all dose group, gender, and study day combinations were provided. Categorical outcomes were summarized by counts and percentages for each dose group for the study days when data were collected. The individual cat was considered the experimental unit. All available data were used in the calculations. Data collected outside of the defined study schedule for diagnostic purposes and/or management of concurrent health issues were not summarized.

Profile plots of continuous variables with repeated measures for each individual animal from baseline to study completion were provided. In addition, means ±standard deviation for each dose group were plotted across time for each outcome. For variables where normal reference ranges were available, the upper and lower limits of the reference range were included on all plots.

Results:

Clinical Observations and Examinations: Immediately following dosing, ear flicking was observed in 45/48 cats from all groups, head shaking was observed in all cats in all groups, and pulling away/flinching occurred in 34/48 cats from all groups. Pulling away and flinching occurred at a higher incidence in the vehicle control (11/16 cats) and 5.3 mg/kg (16/16 cats) groups compared to the 1.1 mg/kg (4/8 cats) and 3.2 mg/kg (3/8 cats) groups. Fractious behavior was observed in three cats in the vehicle control group and five cats total from the 3.2 and 5.3 mg/kg groups. Hypersalivation was reported in one cat in the 1.1 mg/kg group and one cat in the 5.3 mg/kg group. Pawing at the face/ears was observed in all groups.

Application site reactions of the inner and outer pinnae included erythema, alopecia, thickening, and flaking occurred in all cats in the study.

Erythema, crusting, alopecia, and scabbing of the skin, mostly around the head and neck, occasionally affecting the tail, tarsi, or carpi, were frequently reported in 45/48 cats from all groups. These skin abnormalities are likely from cats spreading the ointment to other areas by grooming.

Vomiting occurred infrequently in all groups during the study. Diarrhea occurred in one cat in the vehicle control, one in the 3.2 mg/kg, and two cats in the 5.3 mg/kg groups. Frank blood in the stool was observed in one cat in the vehicle control, two cats in the 3.2 mg/kg group, and one cat in the 5.3 mg/kg group. There is no direct correlation with vomiting or diarrhea and the administration of Mirataz™.

Polyuria was documented frequently in cats from the 3.2 and 5.3 mg/kg groups during the dosing period and occurred in all groups (three cats in vehicle control, two in 1.1 mg/kg, four in 3.2 mg/kg, and nine in the 5.3 mg/kg groups). Polydipsia was reported in one cat in the 5 mg/kg group. Stranguria was observed

in two cats in the vehicle control, one in the 1.1 mg/kg, one in the 3.2 mg/kg, and one in the 5.3 mg/kg groups. Hematuria was reported in all groups during the dosing period only. Eight cats developed cystitis with or without urethral obstruction throughout the study; this included cats from all groups including vehicle control.

Behavior: There were treatment related increases in vocalization, hyperactivity, and attention-seeking behaviors. The 5.3 mg/kg group had higher vocalization scores during the first two weeks and more incidences of vocalization during dosing. The vocalization occurred in fourteen cats in the vehicle control, seven in the 1.1 mg/kg, eight in the 3.2 mg/kg, and thirteen in the 5.3 mg/kg groups. The 5.3 mg/kg group had 40 incidences of hyperactivity compared to 21 in the vehicle control, 15 in the 1.1 mg/kg, and 22 in the 3.2 mg/kg groups. During dosing, the 5.3 mg/kg group had 105 incidences of soliciting attention, compared to 79 in the vehicle control, 41 in the 1.1 mg/kg, and 29 in the 3.3 mg/kg groups. Tremors were observed in at least half of all cats in all groups.

Body Weight and Food Consumption: There were no treatment related clinical effects on body weight and food consumption. Treatment related clinical effects were not expected because the cats were fed a restricted amount of dry food daily.

Electrocardiogram and Blood Pressure: Ventricular premature contractions (VPCs) were noted in one cat each from the 1.1 mg/kg and 5.3 mg/kg groups. The same cat in the 5.3 mg/kg group with VPCs had a right mean electrical axis deviation as well. Tall R waves were noted in one cat in the 1.1 mg/kg group. The correlation between electrocardiogram abnormalities and Mirataz™ is unclear. There were no clinically relevant effects on blood pressure.

Ophthalmic Examinations: There were no clinically relevant effects noted on ophthalmic examinations.

Clinical Pathology: Elevation in eosinophil counts was observed in three cats in the vehicle control, two in the 1.1 mg/kg, and three in the 5.3 mg/kg groups. This finding may relate to the degree of ear pinnae irritation (alopecia, erythema, flaking, and thickening) that was observed.

There were no clinically relevant findings in coagulation.

Elevations in alanine aminotransferase (ALT) occurred in four cats each from the vehicle control (two from recovery group, two non-recovery group), 3.2 mg/kg, and 5.3 mg/kg groups (one from recovery group, three non-recovery group). Three cats only had a single day elevation (two cats in the 3.2 mg/kg group and one in the 5.3 mg/kg group). Four cats had sustained ALT elevations (two or more consecutive high values). On Day 15, a single cat in the 3.2 mg/kg group demonstrated a marked ALT elevation of 3397 U/L (approximately 30X the upper reference range), with concurrent elevations in AST (150 U/L and 114 U/L on Days 15 and 16, respectively) and GGT (9 U/L and 8 U/L on days 15 and 16, respectively). At the last day of dosing, Day 42, the ALT declined to 109 U/L and the AST and GGT returned to within normal limits. Isosthenuria (1.008-1.012 urine specific gravity) occurred only in the Mirataz™ treated groups (one cat each from 1.1 mg/kg, 3.2 mg/kg, and 5.3 mg/kg groups). One cat each from vehicle

control and 3.2 mg/kg groups had bacteriuria; both of these cats were euthanized on Day 35 due to systemic complications from urethral obstruction. Casts and struvite crystals were seen in all groups.

Pharmacokinetics (PK): Samples were analyzed using a validated liquid chromatography tandem-mass spectrometry (LC-MS/MS) method. Individual animal concentration-time data were divided by dose groups and study days, and non-compartmental analysis (NCA) with a uniform weighting scheme was performed using Phoenix® WinNonlin®. The NCA results are summarized in Table III.2. Absorption was more rapid and consistent with repeated doses in which a smaller median T_{max} of 4-6 hours (Day 35) than 5-8 hours (Day 0) was observed. The terminal half-life values were determined based on only 3 cats (1.1 mg/kg group), 4 cats (3.2 mg/kg group) and 2 cats (5.3 mg/kg group) after the first dose, whereas on Study Day 35, terminal half-lives were determined based on all (1.1 mg/kg), and the majority of 3.2 mg/kg and 5.3 mg/kg cats. There was also a minor trend of prolonged terminal half-life with increasing dose. The substantial difference in half-life in 5.3 mg/kg group between Day 0 and 35 may be due to the smaller number of acceptable time points used to generate half-life after the first dose.

The median accumulation of mirtazapine (1.1 mg/kg group) between first dose and 35th dose was 3.71X (based on $AUC_{0\text{-}24hr}$ ratio) and 3.90X (based on C_{max} ratio).

Table III.2. Mean (standard deviation) plasma pharmacokinetic parameters of mirtazapine 2% transdermal ointment in cats calculated by non-compartmental analysis

Dose (mg/kg)	**Day**	**T_{max}[a] (hr)**	**C_{max} (ng/mL)**	**$AUC_{0\text{-}24hr}$ (ng*hr/mL)**	**$t_{1/2}$ (hr)**
1	0	8 (8.55)	18.02 (4.37)	183.90 (77.77)	13.88 (4.53)
	35	6 (1.83)	61.13 (32.44)	790.02 (368.42)	11.16 (2.98)
3	0	5 (3.40)	56.59 (44.16)	626.22 (439.70)	14.70 (9.31)
	35	4 (1.68)	233.64 (121.92)	2350.67 (841.04)	13.95 (3.63)
5	0	8 (4.47)	79.48 (36.40)	1118.83 (366.36)	34.47 (23.42)
	35	4 (3.20)	287.00 (115.12)	3664.96 (861.71)	15.71 (4.29)

[a]T_{max}= time to maximum plasma concentration *(*reported as median)
C_{max} = maximum plasma concentration
$AUC_{0\text{-}24hr}$ = area under the plasma concentration-time curve from time 0 to 24 hr
$t_{1/2}$ = terminal half life

The doses used in the target animal safety study were higher (2.8 to 5.4 mg) than the label dose. Based on dose proportionality in $AUC_{0\text{-}24hr}$ and C_{max} observed in this study, these pharmacokinetic parameters were extrapolated for the 2 mg/cat label dose administered once per day for 35 days (see Table III.3). As shown in the Table, the median time to reach maximum concentration (T_{max}) was 6.0 hours (range, 2 –6 hours); mean ± standard deviation (SD) of peak plasma concentration (C_{max}) was 32.1± 19.9 ng/mL; mean ± SD of half-life of mirtazapine was 11.2±2.98 hours; and mean± SD of area under the concentration-time curve to 24 hours ($AUC_{0\text{-}24hr}$) was 410.3 ±213.5 ng*hr/mL.

Table III.3. Plasma pharmacokinetic parameters at steady state after 2 mg/cat dose of mirtazapine 2.0% transdermal ointment in healthy cats

Parameter[a]	**Unit**	**Mean (SD)**
C_{max}	ng/mL	32.1 (19.9)
T_{max}	hr	6 (2-6)[a]
AUC_{0-24hr}	hr*ng/mL	410.3 (213.5)
Half-life	hr	11.2 (2.98)[b]

C_{max} = extrapolated maximum plasma concentration
[a]T_{max} = time to maximum plasma concentration (reported as median and range)
AUC_{0-24hr} = extrapolated area under the plasma time vs. concentration curve
[b]The half-life value is reflective of both transdermal and oral exposure. In another study where cats wore an Elizabethan collar to restrict access to their ears and consequent oral exposure, a longer half-life (Mean= 20.7 hr) was observed

Mirtazapine trough levels in all mirtazapine treated groups were relatively stable beyond Day 14, suggesting achievement of steady state. Detectable levels of mirtazapine were present in samples collected from the 5.3 mg/kg group in the recovery period on Days 56 and 69, with an average value of 1.05 ng/mL.

Viability: Two cats, one from the vehicle control and one from the 3.2 mg/kg groups, were euthanized early on Day 35 due to complications of urinary bladder obstruction. Two cats, one from the vehicle control and one from the 5.3 mg/kg groups, were euthanized one day earlier than scheduled due to complications of cystitis and urinary bladder obstruction.

Necropsy Examination: Hyperplastic dermatitis of the pinna was observed in all 48 cats. Two male cats from vehicle control, one male cat from 3.2 mg/kg, and one male cat from 5.3 mg/kg groups showed urinary lesions consistent with cystitis (focal or multifocal mucosal hemorrhage of the urinary bladder, mottled-dark red appearance, and irregular contour).

Organ Weights: There is a dose dependent numerical decrease in mean liver weights. The clinical relevance is unknown. However, the drug is metabolized by the liver and there were reported liver enzyme elevations (see Clinical Pathology above).

Histopathology: Treatment-related microscopic findings consisting of epidermal hyperplasia with or without superficial dermatitis and multifocal inflammatory responses were present at the dose site (inner and outer pinnae) in all 48 cats. Cystitis was confirmed in the four male cats diagnosed at gross examination. Urinary tract infection was diagnosed in two vehicle control cats and 1 cat each from the 3.2 mg/kg and 5.3 mg/kg groups. Nephrocalcinosis was reported in all dose groups (3 cats in the vehicle control, 1 cat in the 1.1 mg/kg group, 3 cats in the 3.2 mg/kg group, and 1 cat in 5.3 mg/kg group). Pyelonephritis, consistent with an ascending urinary tract infection, was documented in two vehicle control cats, and one 5.3 mg/kg cat. Necrosis of the kidneys, either papillary or ischemic, was found in one vehicle control cat and one 3.2 mg/kg cat. Unilateral hypoplasia of the thyroid gland was observed in two 5.3 mg/kg cats and unilateral hypertrophy was only seen in one 5.3 mg/kg cat.

Recovery Period
In the recovery period, the observation rates for application site reactions demonstrated notable reductions but not complete resolution in both vehicle control and 5.3 mg/kg dose groups. Application site erythema and flaking resolved completely in the vehicle control and improved in the 5.3 mg/kg groups. Ear thickening improved in both groups. The three recovery cats (two from vehicle control and one from 5.3 mg/kg groups) that had ALT elevations during dosing, resolved. Polyuria reduced in recovery and only occurred one to two times in two cats in the 5.3 mg/kg group.

Conclusions:

This study demonstrated an adequate safety margin to support the use of 2 mg per cat of Mirataz™ transdermal ointment applied to the inner pinna for 14 days for the management of weight loss in cats. Observations related to the test article and vehicle control include dose site reactions (flaking, erythema, crusts, alopecia, thickening) and effects on the urinary system (signs of cystitis: hematuria, stranguria, urethral obstructions). Observations related to the test article include increased vocalization, soliciting attention, hyperactivity/frantic behaviors, tremors, increased ALT liver values, polyuria, polydipsia, hypersalivation, isosthenuria, frank blood in the stool, and diarrhea. The effects on vomiting and the electrocardiograms are unclear. Upon discontinuation of Mirataz™, body weight and food consumption declined and changes to the dose sites improved but did not resolve. Randomization was not conducted in this study. Therefore, this study alone was not used to support the safety of Mirataz™ (mirtazapine transdermal ointment) in cats.

B. Comprehensive Evaluation of Safety

A comprehensive safety review was performed on six pilot studies (five laboratory and one clinical study) utilizing the final market formulation of Mirataz™ (mirtazapine transdermal ointment) in cats, and one laboratory study that did not use final market formulation. These studies included proof of concept, pilot safety, pilot effectiveness, and PK studies.

1. **Title:** A Multicenter, Randomized, Single-Blind, Placebo-Controlled Pilot Study of Topical Mirtazapine for Stimulation of Weight Gain in Cats. (Study No. KB104P)

   Study Summary: In this multicenter, randomized, single-blind, placebo-controlled pilot study, 32 client-owned cats (19 male neutered and 13 female spayed) ranging in age from 4-20 years were randomized to receive either a dose of approximately 2 mg/cat mirtazapine (10 male neutered and 6 female spayed cats) or vehicle control (nine male neutered and 7 female spayed cats) topically on the pinna of the ear, once daily for approximately 28 days (±3 days).

   Safety Observations: Five out of 16 cats administered mirtazapine and only 2/16 cats administered vehicle control vomited. Two out of 16 cats administered mirtazapine and none of the vehicle control cats had diarrhea. Three of 16 (19%) cats administered mirtazapine showed either inflammation at the application site or itchy/warm ears; and 2 of 16 (13%) vehicle control

cats had inflammation at the application site. One cat (6%) administered mirtazapine had elevated creatinine. One cat (6%) administered mirtazapine had progression of chronic renal failure. One cat administered mirtazapine showed aggression.

2. **Title:** A Pilot Laboratory Safety Study of 2% Mirtazapine Ointment Administered Topically (Transdermally) to Adult Cats at 5x the Target Therapeutic Dosage. (Study No. KB108T)

   Study Summary: In this non-randomized, unmasked, terminal, non-GLP pilot safety study, seven intact female cats received 5.3 mg/kg mirtazapine topically on the inner pinna of the ear once daily for 28 days. On Day 28, all cats were humanely euthanized and gross and histopathologic examinations were performed. This study dosed mirtazapine topically at 8.3-10.2X the labeled dose.

   Safety Observations: All seven cats had mild redness of both ears and flaking. Two cats had scabs present in the ears. One cat had spasms in the hind-end and ataxia on Days 20 and 21. Two cats vomited; one cat vomited on Day 21 and the other cat vomited Days 15 through 20. Two cats had polyuria on Day 4, each with a normal urine specific gravity value (1.023 and 1.037). Five cats developed a sinus tachycardia on Day 13 that was not present at baseline. Two cats had QRS complexes that were tall, indicative of possible left ventricle enlargement on Day 13. For one of these two cats, this finding resolved by the end of the study. One cat developed a mild left axis shift at the end of the study. One cat with a right axis shift noted at baseline was mildly hypertensive with average blood pressures of 185, 189, and 191 mmHg on Days -5, 13, and 27, respectively. Three cats had mildly enlarged popliteal lymph nodes during treatment. Pathology results showed epidermal hyperplasia and dermal inflammation in all seven cats.

3. **Title:** A Laboratory, Randomized, Effectiveness and Pharmacokinetic Study of Topically (Transdermal) Administered Mirtazapine Ointment at 0.5 mg/kg and 2 mg/kg in Adult Cats. (Study No. KB111PK)

   Study Summary: In this randomized, masked, pilot, non-GLP study, 20 adult (10 males and 10 females) cats received either 0.5 mg/kg mirtazapine, 2.1 mg/kg mirtazapine, or no treatment (negative control) topically on the inner pinna once daily for 14 days.

   Safety Observations: Mild redness and flaking of the pinna occurred in all mirtazapine treated cats. In the 0.5 mg/kg group, one cat had a tremor/twitch in the right shoulder on Day 1, one cat had diarrhea on Day 2, one cat vomited food twice on Days 12 and 17, one cat developed a grade 3/6 heart murmur on Day 18, and one cat had alopecia on the left shoulder on Day 18. In the 2.1 mg/kg group, two cats had a lesion/cut on the ear, one cat vomited food on Day 8, one cat had poor food consumption on Days 5 through 17, one cat had nasal discharge on Day 17, one cat had an expiratory wheeze noted and upper respiratory infection diagnosed on Day 18, and one cat had a small area of alopecia and scabbing on ventral chin on Day 18.

4. **Title:** A Laboratory, Randomized, Cross-Over Pharmacokinetic Study of Orally and Topically (Transdermal) Administered Mirtazapine 2% Ointment In Adult Cats. (Study No. KB103PK)

   Study Summary: In this randomized, blinded, crossover, non-GLP pilot pharmacokinetic study, 8 cats (two male neutered and six female spayed) received a single dose of 0.5 mg/kg (0.66-2.3X) mirtazapine ointment. On Day 0, four cats received 0.5 mg/kg orally by gavage and four cats received 0.5 mg/kg topically on the right ear pinna. On Day 5, the treatment administration methods were crossed over. The cats were dosed without regard to the prandial state and were required to wear Elizabethan collars.

   Safety Observations: When administered orally, two cats salivated for less than 4 minutes and six cats had lip licking, lasting for 13 minutes in one cat. One cat vomited on two separate days during the study, once during oral administration and once during topical (transdermal) administration. One cat had one episode of diarrhea on Day 5 after oral administration. One cat developed a moist dermatitis and an open sore around her rectum after oral administration. One cat developed a mild upper respiratory tract infection and irritation of the right eye after oral administration. On Day 9, six cats had serous discharge from both eyes (three cats after oral administration and three cats after topical administration), one cat had a mildly enlarged right popliteal lymph node after topical administration, and one cat had a dry flaky coat after topical administration. There were no clinically relevant behavioral changes.

5. **Title:** Laboratory, Safety Study of Topical (Transdermal) Mirtazapine 2% Ointment Dosed Orally in Cats at 5X the Targeted Label Dose. (Study No. KB110)

   Study Summary: In this open label, pilot safety study, five adult cats (2 male neutered and 3 female spayed) were orally administered one 10.6 mg/cat dose (5.3X the labeled dose) of mirtazapine ointment.

   Safety Observations: Mild to moderate salivation was observed in all cats. One cat sneezed and one cat vomited food. One cat developed stranguria and was diagnosed with a urinary tract infection.

6. **Title:** Determination of KIND-010 2% Ointment Dislodged upon Petting Following Repeated Topical (Transdermal) Administration in Cats. (Study No. KB119)

   Study Summary: In this GLP, one-group, one-treatment, multi-dose design pilot study, eight adult female cats received approximately 2 mg/cat of mirtazapine ointment topically on the right ear inner pinna once daily for 14 days.

   Safety Observations: One cat became agitated/aggressive. Five cats pawed or scratched at the right ear and licked their paw at dosing. All eight cats developed redness of the pinna, two with blood on the pinna.

7. **Title:** Laboratory Study: Randomized, Multi-dose Pharmacokinetics, Pharmacodynamics, and Tolerance Study of Two Doses of Mirtazapine Administered Topically (Transdermally) to Adult Cats. (Study No. KB101PK)

   Study Summary: In this pilot pharmacokinetic/pharmacodynamic pilot study utilizing non-final market formulation, 20 non-naïve laboratory adult cats (10 male and 10 female) were randomized to receive either 0.5 mg/kg of 2% mirtazapine ointment, 1.1 mg/kg of 4% mirtazapine ointment, or vehicle control topically on the ear pinna once daily for 14 days.

   Safety Observations: One cat in the high dose group became ill and was found moribund 65 days after the last dose of study drug. The cat had lost significant weight, and post-mortem evaluation with histopathology led to a diagnosis of hepatic lipidosis and bacterial enteritis. The cat did not lose weight between Days 14 and 28 of the study and food intake was similar to other cats during the entire study period.

   Nineteen out of twenty cats had flaking of the pinna and all twenty cats had redness of the pinna. Increased vocalization was observed in 17 cats and struggling was observed in 4 cats. One cat in the high dose group had a mild twitch/bobble. One cat in the high dose group had labored breathing that persisted after the study and developed sporadic loose stools with occasional blood, ocular discharge, a swollen left eye, and a red, raw anus. Five cats in the low dose group had blood in the stool on different study days. There were no consistent trends in blood pressure.

Conclusions:

Overall, safety data collected among these additional seven pilot studies did not identify any significant safety concerns when mirtazapine was administered at the recommended label dose. The findings in all seven studies are consistent with the clinical field study and the six-week laboratory margin of safety study, and support the safe use of mirtazapine when administered transdermally on the pinna at 2 mg/cat for 14 days in cats.

IV. HUMAN FOOD SAFETY

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

V. USER SAFETY

A. Product Labeling

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Mirataz™:

Not for human use. Keep out of reach of children.

Wear disposable gloves when handling or applying Mirataz™ to prevent accidental topical exposure. After application, dispose of used gloves and wash hands with soap and water. After application, care should be taken that people

or other animals in the household do not come in contact with the treated cat for 2 hours because mirtazapine can be absorbed transdermally and orally. However, negligible residues are present at the application site and the body of the cat at 2 hours after dosing.

In case of accidental skin exposure, wash thoroughly with soap and warm water. In case of accidental eye exposure, flush eyes with water. If skin or eye irritation occurs seek medical attention.

In case of accidental ingestion, or if skin or eye irritation occurs, seek medical attention.

B. Determination of the 2-Hour No-Contact Time with the Treated Cat

Human users may be exposed to mirtazapine residues through hand contact (both adults and toddlers) and/or hand-to-mouth contact (toddlers) when petting the treated cat. A no-contact time with the treated cat can prevent human users from being exposed to mirtazapine residues above the safety level. The following user safety risk assessment utilizing a margin-of-exposure (MOE) approach demonstrates that residues measured at 2-hour post-application are unlikely to cause safety concerns to human users. Therefore, the labeling includes a 2-hour no-contact time with the treated cat to assure human user safety.

1. An MOE approach for user safety risk assessment

   An MOE is a common tool used to determine human user risk from exposure to drug residues. An MOE is the ratio between the highest dose without adverse effects (i.e., no-observed-adverse-effect level or NOAEL) observed in laboratory animals or humans to the estimated human exposure to drug residues. The higher the MOE, the less likely a drug is to pose a safety concern. In general, when an MOE is no less than 100 (meaning that the estimated human exposure to drug residues is at least 100-fold less than the amount of drug residues needed in causing an adverse effect(s)), human users are considered to have little risk of adverse effects from exposure to drug residues.

2. Calculations of MOEs (NOAEL divided by estimated human exposure)

   Determination of the NOAEL: Based on toxicology data from laboratory animals and the human medicinal use of mirtazapine, the NOAEL selected for the MOE calculation was 0.25 mg/kg body weight (bw)/day, derived from the human clinical dose of mirtazapine (15 mg/day for up to 40 weeks for an average adult weight of 60 kg).

   Estimated human exposure: The human exposure was estimated based on the amount of mirtazapine residues present on the skin of the treated cat from a wipe test study, and assuming a worst-case of 100% bioavailability and absorption through human skin or hand-to-mouth oral ingestion. In a wipe test study entitled, "Determination of KIND-010 2% Ointment Dislodged upon Petting Following Repeated Topical (Transdermal) Administration in Cats" (Study No. KB119), the dislodged mirtazapine residues were measured at the application site (ear) and the body of the cat at 0, 0.5, 1, 2, and 4 hours following topical administration of 2 mg mirtazapine.

Calculations of MOEs: MOEs were calculated for each time point post-application for both adults and toddlers, by dividing the NOAEL of 0.25 mg/kg bw/day by the estimated adult or toddler exposure at each time point post-dosing (see Table V.1. below).

Table V.1. Margin-of-Exposure (MOE) calculations for human users exposed to mirtazapine residues when petting the treated cat.

Time post-dosing (hour)	Adult exposure* (µg/kg bw/day)	Toddler exposure** (µg/kg bw/ day)	MOE*** (adults)	MOE*** (toddlers)
0	33	133	7.5	1.9
0.5	6.8	27.3	36.8	9.2
1	0.83	3.31	301	75.8
2	0.50	1.98	500	126

* Adult exposure = (dislodged mirtazapine residues x 100% bioavailability)/60 kg adult weight
** Toddler exposure= (dislodged mirtazapine residues x 100% bioavailability)/15 kg toddler weight;
*** MOE = NOAEL/adult or toddler exposure; NOAEL = 0.25 mg/kg bw/day (*i.e.*, 250 µg/kg bw/day)

As shown in Table V.I above, 2 hours for no-contact with the treated cat post-application provides an MOE of 500-fold for adults and an MOE of 126-fold for toddlers. This means that the estimated human exposure is expected to be at least 100-fold lower than the amount of mirtazapine residues needed to cause adverse effects. As stated above, an MOE of 100 ensures there is little concern to human users. Therefore, a 2-hour no-contact time with the treated cat is considered sufficient to assure human user safety.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Mirataz™, when used according to the label, is safe and effective for the management of weight loss in cats.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly assess weight loss and provide guidance for the management of weight loss in cats. Furthermore, professional expertise is required to monitor for and respond to adverse reactions, including adverse effects that may occur after cessation of the drug.

B. Exclusivity

Mirataz™, as approved in this approval letter, qualifies for FIVE years of marketing exclusivity beginning as of the date of this approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the FD&C Act because this is the first

time we are approving this active ingredient in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information:

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