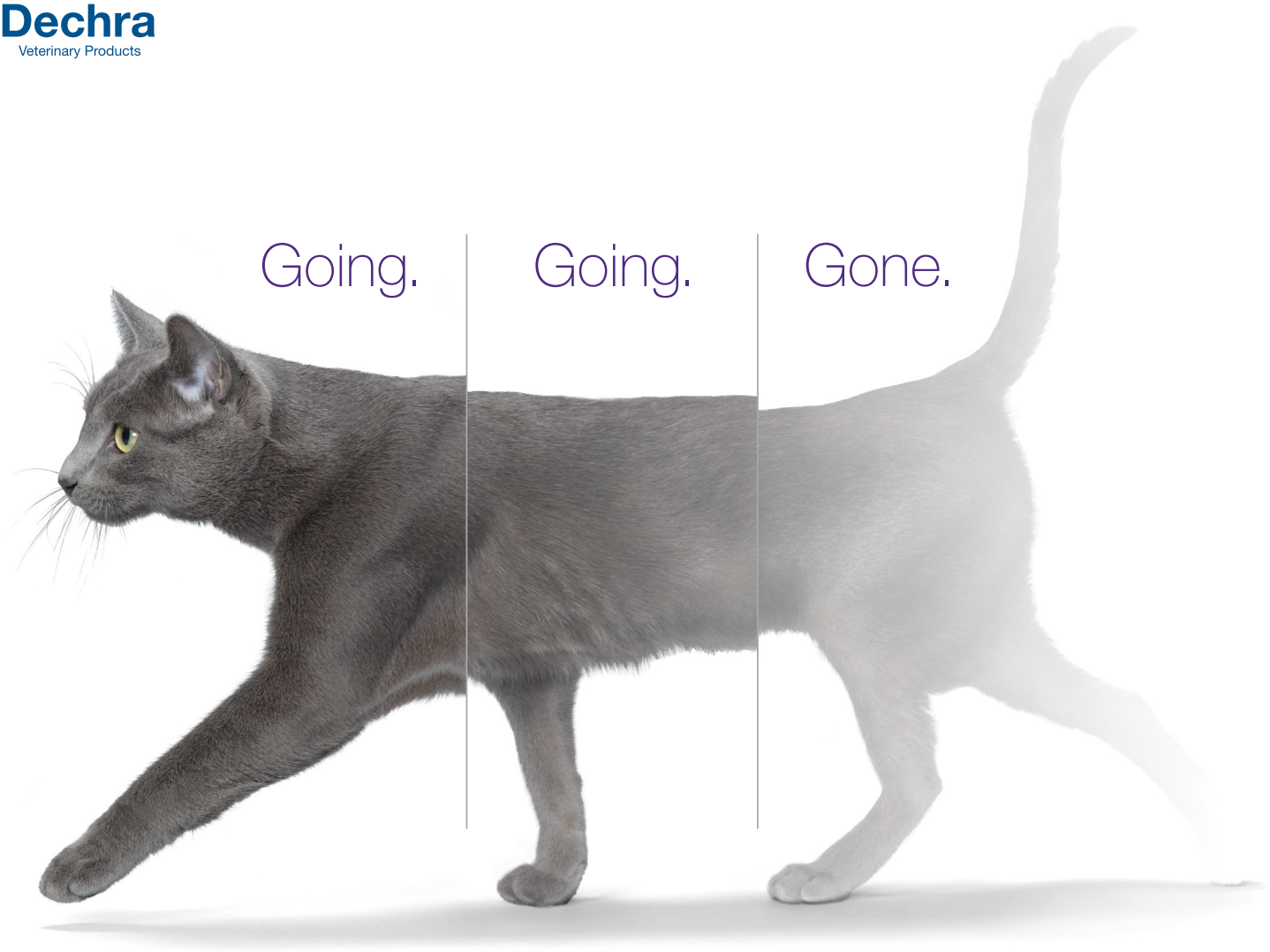
Dechra
Veterinary Products



With unintended weight loss, you can't afford to wait.

Take control with Mirataz® (mirtazapine transdermal ointment).

The first and only FDA-approved transdermal medication for the management of weight loss in cats.

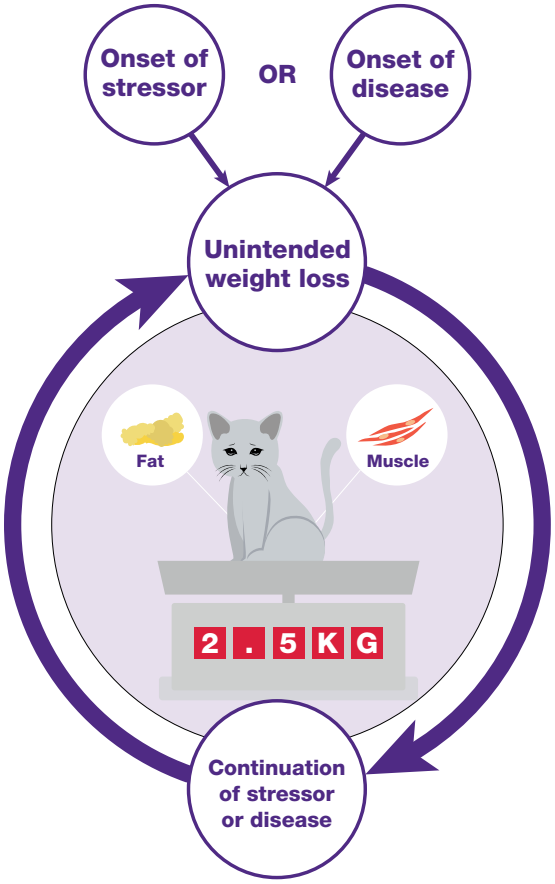
Mirataz®
(mirtazapine transdermal ointment)

Identifying causes of feline weight loss

Feline weight loss is often associated with underlying conditions

Some of the more common underlying diseases could be[1-3]:

- Hyperthyroidism
- Chronic kidney disease
- Inflammatory bowel disease
- Neoplasia
- Pancreatitis
- Liver failure



Weight loss can also be linked to non–disease-related stressors

Changes in environment, stress from travel or medical procedures, or even changes in food can all affect a cat's eating habits.

Prolonged inadequate nutrition may be more detrimental to the patient than the primary disease process[4]

Therefore, both identifying weight loss and diagnosing the underlying cause are important.

After identifying changes in eating behavior, body weight, and body condition and discussing them with the cat owner, veterinarians can initiate a tailored diagnostic plan, guided by a thorough history and physical exam.

Important Safety Information

Mirataz® (mirtazapine transdermal ointment) is for topical use in cats only under veterinary supervision. Do not use in cats with a known hypersensitivity to mirtazapine or any of the excipients. Do not use in cats treated with monoamine oxidase inhibitors (MAOIs). Not for human use. Keep out of reach of children. Wear gloves when handling/applying, wash hands after and avoid contact between the treated cat and people or other animals for 2 hours following application. Use with caution in cats with hepatic and kidney disease. Cat's food intake should be monitored upon discontinuation. Safety has not been evaluated in cats less than 2 kg, less than six months of age or in breeding, pregnant or lactating cats. The most common adverse reactions observed during clinical trials were application site reactions, behavioral abnormalities (vocalization and hyperactivity) and vomiting.

For product label, including complete safety information, see pages 10-11.

Miratraz® (mirtazapine transdermal ointment)

A survey of US veterinarians indicated that

~9,000,000 CATS

PRESENT WITH WEIGHT LOSS/INAPPETENCE DUE TO UNDERLYING CONDITIONS[5-6]

7 MILLION

OF THOSE CATS WERE NOT PRESCRIBED A MEDICATION

(compounded or human generic mirtazapine) to manage their weight loss[5-6]

74% OF VETERINARIANS indicated that the ease of administering a medication is one of the most important factors in selecting a medication for the management of weight loss in cats[5]

With Miratraz, veterinarians can confidently recommend an effective topically applied product for cats with unintended weight loss

While not FDA-approved, human and compounded versions of mirtazapine have been used off-label but may not be ideal for most cats

- Human tablets must be split or broken, which may result in:
  - Inaccurate dosing, which has been shown to result in accidental overdose and toxicity[7]
  - Unknown user safety to humans handling cut or broken pills
  - Unknown drug distribution in pill fragments
- Oral products placed on food will work only if the cat is eating and fed individually
- Liquids by mouth may not be any easier than pilling
- Compounded transdermal mirtazapine has been shown to result in variable and inconsistent [gel] concentrations[8]

Miratraz gives your clients an option for one less oral medication for their cats

The first FDA-approved transdermal medication available for cats

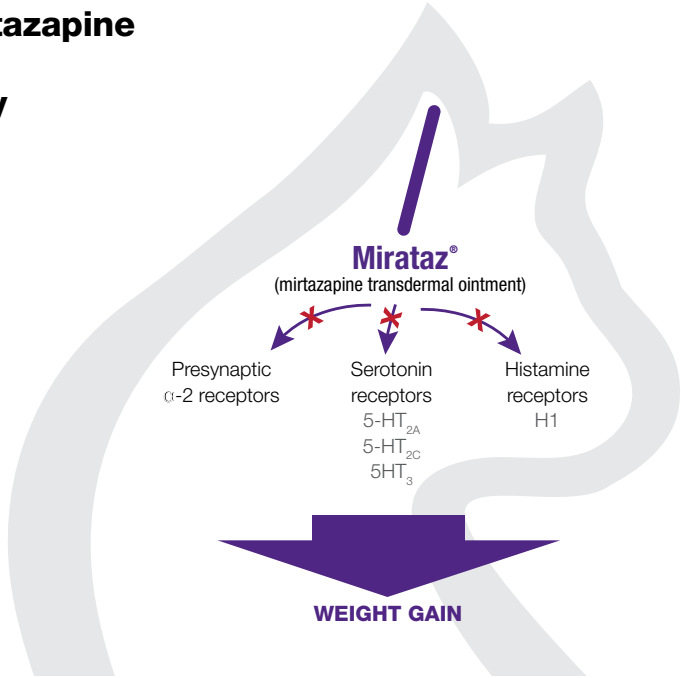
The active ingredient in Mirataz is mirtazapine

Mirataz is classified pharmacologically as a weight gain drug

The pharmacodynamic action of mirtazapine involves antagonism of several receptor sites

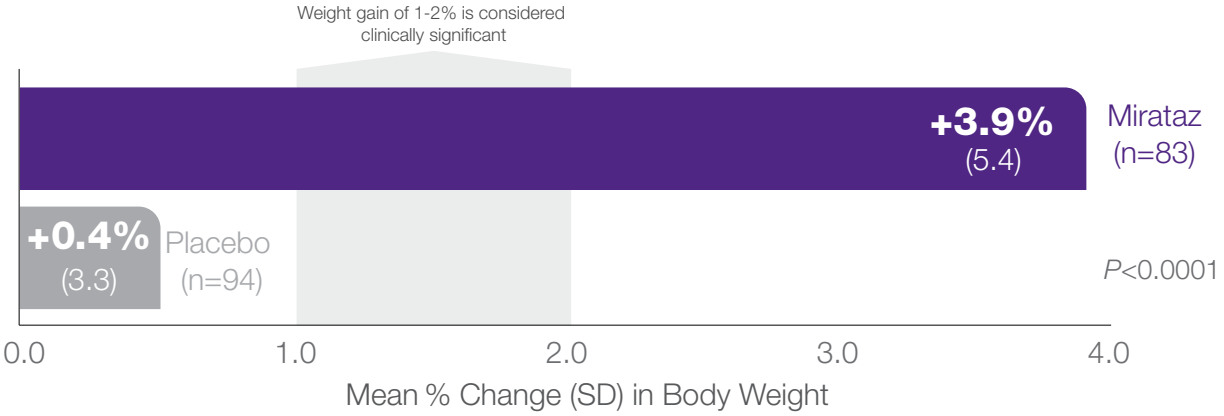
Antagonism of presynaptic α-2 receptors, serotonin receptors (5-HT_{2A}, 5-HT_{2C}, 5-HT_3), and histamine receptors (H1) by mirtazapine has been demonstrated to result in:

- Orexigenic effect via interaction with nuclei within the hypothalamus[4]
- Enhanced release of both serotonin (5-HT) and noradrenaline (NE)[9]



Mirataz demonstrated a 3.9% increase in body weight in cats with unintended weight loss in as little as 14 days[10]

WEIGHT GAIN IN CATS WITH MIRATAZ VS PLACEBO



STUDY DESIGN: Randomized, double-blind, placebo-controlled study (N=177)

Important Safety Information

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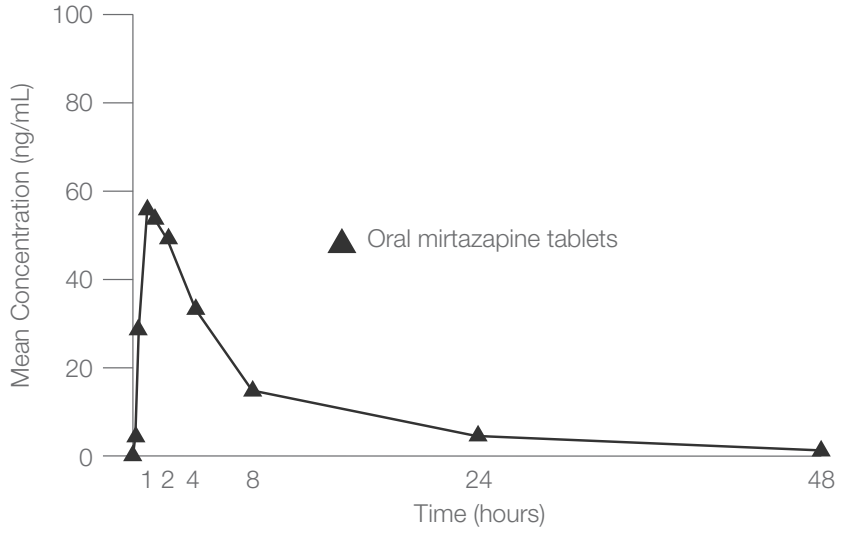
For product label, including complete safety information, see pages 10-11.

Effectiveness of Mirataz®
(mirtazapine transdermal ointment)

The off-label use of human mirtazapine tablets given orally to cats is based on extrapolation with no species-specific PK to support dosing[11]

COMBINED PHARMACOKINETIC CURVE IN HEALTHY CATS ADMINISTERED 1.88 MG OF MIRTAZAPINE ORALLY*†

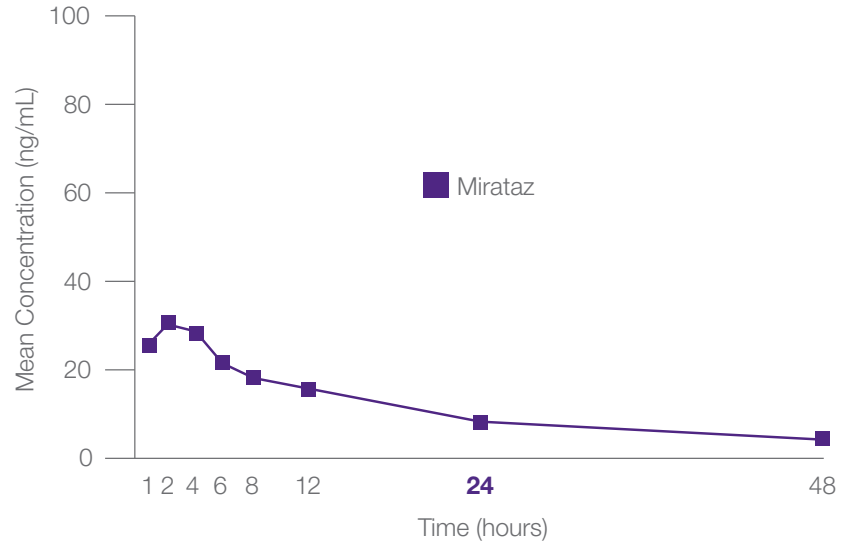


*Number of cats sampled: n=5 (0.25h); n=6 (1.5h, 2h); n=11 (0.5h, 8h, 48h); n=21 (4h); n=22 (1h, 24h)
†Data first reported and reproduced with permission[12-14]

Mirataz, the FDA-approved mirtazapine transdermal ointment, has a similar elimination half-life to oral mirtazapine, but a lower C_{max}, lower AUC, and longer T_{max}[15,16]

Pharmacokinetic data in cats supports daily dosing. In cats with kidney or liver disease, it is desirable to limit peak serum concentrations and AUC to minimize drug exposure where metabolism and elimination or clearance may be impacted by organ function while still maintaining clinical effect.

MIRATAZ CONCENTRATIONS IN CATS AT STEADY STATE FOLLOWING DAILY DOSING (DAY 13; 0.5 MG/KG)



Mirataz® (mirtazapine transdermal ointment) safety profile

230 cats were enrolled in a field study to assess the clinical safety and effectiveness of Mirataz. Cats enrolled in the study with underlying disease may have received concurrent medications.[10]

PRE-EXISTING CONDITIONS AND RELEVANT MEDICAL HISTORY OF CATS ENROLLED IN THE STUDY (SAFETY POPULATION)[17]

Pre-existing Condition	Mirataz N=115 n (%)	Placebo N=115 n (%)
Renal	64 (55.7%)	48 (41.7%)
Multisystemic	56 (48.7%)	48 (41.7%)
Dental	35 (30.4%)	39 (33.9%)
Gastrointestinal	31 (27.0%)	35 (30.4%)
Cardiovascular	25 (21.7%)	25 (21.7%)
Endocrine	24 (20.9%)	19 (16.5%)
Urinary	23 (20.0%)	32 (27.8%)
Musculoskeletal	22 (19.1%)	14 (12.2%)
Skin and aural	20 (17.4%)	15 (13.0%)
Behavioral	11 (9.6%)	16 (13.9%)
Respiratory	8 (7.0%)	17 (14.8%)
Hepatobiliary	8 (7.0%)	4 (3.5%)

CONCOMITANT MEDICATIONS ADMINISTERED (OCCURRING IN >3% OF CATS IN ANY TREATMENT GROUP [SAFETY POPULATION])[18]

Concomitant Medication Category	Mirataz N=115 n (%)	Placebo N=115 n (%)
Parenteral fluids	20 (17.4%)	15 (13.0%)
Antibiotic	19 (16.5%)	24 (20.9%)
Vitamin/Mineral	18 (15.7%)	18 (15.7%)
Corticosteroid	13 (11.3%)	7 (6.1%)
Anti-thyroid drug	12 (10.4%)	9 (7.8%)
Supplement	9 (7.8%)	16 (13.9%)
Anti-hypertensive	8 (7.0%)	9 (7.8%)
Vaccine	7 (6.1%)	10 (8.7%)
Opioid	6 (5.2%)	8 (7.0%)
Antacid	6 (5.2%)	6 (5.2%)
Antiemetic	6 (5.2%)	5 (4.3%)
Anthelmintic or Antiparasitic	5 (4.3%)	15 (13.0%)
Laxative	4 (3.5%)	5 (4.3%)
NSAID	4 (3.5%)	1 (0.9%)

The most common adverse events observed in the clinical field study included application-site reactions, vocalization, hyperactivity, and vomiting.[19]

- Of the cats in the clinical field study, 27.8% had pre-existing vomiting at the time of enrollment due to underlying conditions[10]

ADVERSE EVENTS REPORTED DURING THE CLINICAL FIELD STUDY (OCCURRING IN >3% OF CATS IN THE MIRATAZ GROUP [SAFETY POPULATION])[16,19]

Description of Adverse Event	Mirataz N=115 n (%)	Placebo N=115 n (%)
Application Site (ear pinna)		
Erythema	12 (10.4%)	20 (17.4%)
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, or weakness)	4 (3.5%)	9 (7.8%)
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%)
Inappetence	5 (4.3%)	5 (4.3%)
Renal insufficiency	4 (3.5%)	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

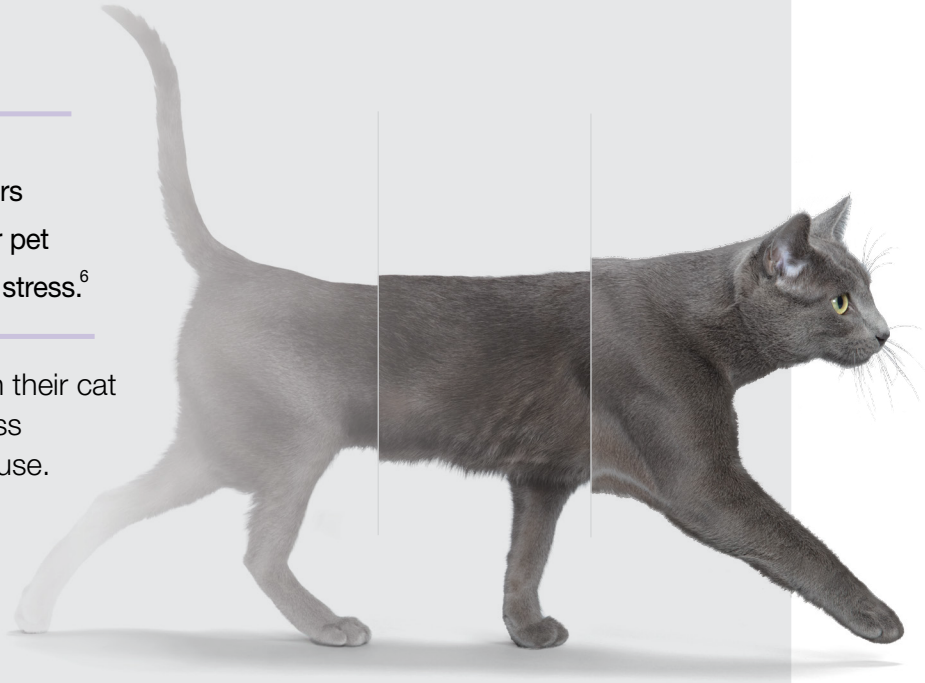
- Elevated BUN levels were not considered clinically relevant and were likely due to the increased incidence of renal disease (based on clinical pathology and urinalysis) at the time of enrollment in the Mirataz group[10]

Unintended weight loss can have significant consequences

Pets bring joy to our lives

In fact,

67% of pet owners believe their pet helps lower stress.[6]



Pet owners become worried when their cat experiences unintended weight loss associated with any underlying cause.

It's a challenge to ensure at-home treatment plans address both the cat's medical needs and protect the human-animal bond.

Ideal body condition correlates to survival

Analyzing patient records of more than 2,600 cats showed **a body condition score (BCS) of 6 had the highest survival probability. Lifespan *decreased* when cats had a BCS less than 5 out of 9.**[20]

This supports other research that shows being underweight puts cats at risk for damage to internal organs and increased susceptibility to infections.[21]

Helping clients identify the underlying causes of weight loss and maintaining their cat's ideal body condition may help improve their pet's lifespan and quality of life.

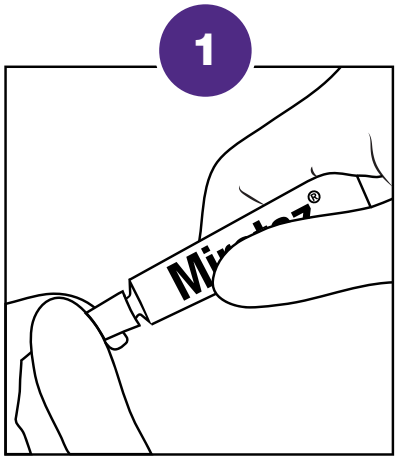
Important Safety Information

Mirataz® (mirtazapine transdermal ointment) is for topical use in cats only under veterinary supervision. Do not use in cats with a known hypersensitivity to mirtazapine or any of the excipients. Do not use in cats treated with monoamine oxidase inhibitors (MAOIs). Not for human use. Keep out of reach of children. Wear gloves when handling/applying, wash hands after and avoid contact between the treated cat and people or other animals for 2 hours following application. Use with caution in cats with hepatic and kidney disease. Cat's food intake should be monitored upon discontinuation. Safety has not been evaluated in cats less than 2 kg, less than six months of age or in breeding, pregnant or lactating cats. The most common adverse reactions observed during clinical trials were application site reactions, behavioral abnormalities (vocalization and hyperactivity) and vomiting.

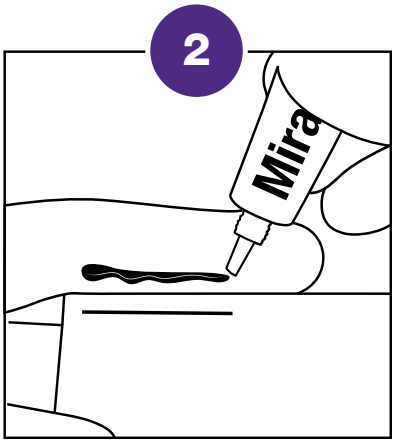
For product label, including complete safety information, see pages 10-11.

Dosing and administration

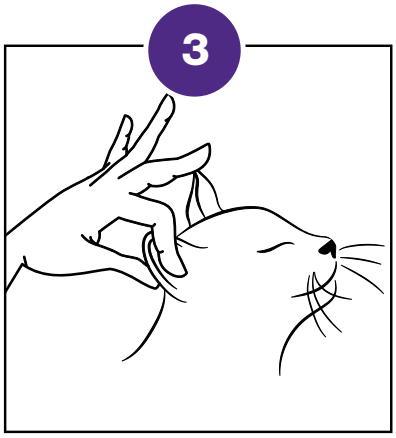
Administer topically by applying a 1.5-inch ribbon of ointment (approximately 2 mg/cat, equal to 0.1 mL) on the inner pinna of the cat's ear once daily for 14 days (see diagrams below)



Step 1:
Wear disposable gloves. Twist cap on tube counterclockwise to open.

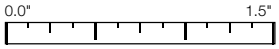


Step 2:
Apply even pressure on tube and squeeze a 1.5-inch line of ointment onto your gloved finger using the measured line on the carton or in the package insert.



Step 3:
Using your gloved finger, gently rub ribbon of ointment on inside pinna of the cat's ear spreading it evenly over the surface. Dispose of used gloves after each application. If contact with your skin occurs wash thoroughly with soap and warm water.

Example of 1.5" application.



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.

To see how convenient Mirataz is to apply, go to *mirataz.com/mirataz/dosing-and-administration/* or scan the QR code.

Miratаz®
(mirtazapine transdermal ointment)

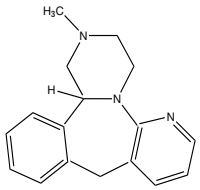
Each 1 g of Miratаz contains 20 mg mirtazapine (2%). Each 5 g tube contains 100 mg (0.1 g) of mirtazapine.

For topical application in cats only. Not for oral or ophthalmic use.

CAUTION:
Federal law (USA) restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:
Miratаz (mirtazapine transdermal ointment) is a white to off-white ointment containing 2% (w/w) of mirtazapine suitable for transdermal (topical) administration. Miratаz contains the following inactive ingredients: Polyethylene Glycol (PEG) 400, PEG 3350, Diethylene Glycol Monoethyl Ether, PEG-8 Caprylic/Capric Glycerides, Oleyl Alcohol, Butylated Hydroxytoluene, Dimethicone, and Dry Flo TS.

The structural formula of mirtazapine is:



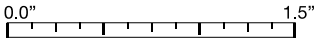
Molecular Formula: $C_{17}H_{19}N_3$ Molecular Weight: 265.35

INDICATION:
Miratаz is indicated for the management of weight loss in cats.

DOSAGE AND ADMINISTRATION:
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 (see Diagrams below).
Wear disposable gloves when applying Miratаz. Dispose of used gloves after each application.

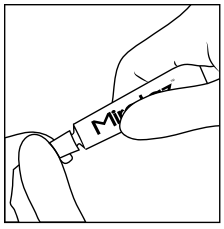
Alternate the daily application of Miratаz between the left and right inner pinna of the ears. Do not administer into the external ear canal. If desired, the inner pinna of the cat's ear may be cleaned by wiping with a dry tissue or cloth immediately prior to the next scheduled dose. If a dose is missed, apply Miratаz the following day and resume daily dosing.

To demonstrate the method of administering the dose, the veterinarian or trained personnel at the clinic should apply the first dose in the presence of the owner.

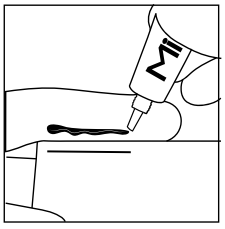


This ruler measures 1.5 inches. Use this ruler to measure the 1.5 inch ribbon of ointment to be applied.

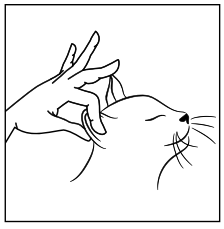
To apply Miratаz:



Step 1: Wear disposable gloves. Twist cap on tube counterclockwise to open.



Step 2: Apply even pressure on tube and squeeze a 1.5-inch line of ointment onto your gloved finger using the measured line on the carton or in this package insert.



Step 3: Using your gloved finger, gently rub ribbon of ointment on inside pinna of the cat's ear spreading it evenly over the surface. Dispose of used gloves after each application. If contact with your skin occurs wash thoroughly with soap and warm water.

CONTRAINDICATIONS:
Miratаz is contraindicated in cats with a known hypersensitivity to mirtazapine or to any of the excipients.

Miratаz should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor (MAOI) [e.g. selegiline hydrochloride (L-deprenyl), amitraz], as there may be an increased risk of serotonin syndrome.

HUMAN WARNINGS:
Not for human use. Keep out of reach of children.

Wear disposable gloves when handling or applying Miratаz 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.

PRECAUTIONS:
Do not administer orally or to the eye.

Use with caution in cats with hepatic disease. Mirtazapine may cause elevated serum liver enzymes (See Animal Safety).

Use with caution in cats with kidney disease. Kidney disease may cause reduced clearance of mirtazapine which may result in higher drug exposure.

Upon discontinuation of Miratаz, it is important to monitor the cat's food intake. Food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days, or if the cat stops eating for more than 48 hours, reevaluate the cat.

Miratаz has not been evaluated in cats < 2 kg or less than 6 months of age.
The safe use of Miratаz has not been evaluated in cats that are intended for breeding, pregnant, or lactating cats.

ADVERSE REACTIONS:
In a randomized, double-masked, vehicle-controlled field study to assess the effectiveness and safety of mirtazapine for the management of weight loss in cats, 115 cats treated with Miratаz and 115 cats treated with vehicle control were evaluated for safety. The vehicle control was an ointment containing the same inert ingredients as Miratаz without mirtazapine. The most common adverse reactions included application site reactions, behavioral abnormalities (vocalization and hyperactivity), and vomiting. The adverse reactions observed in the study and number of cats experiencing each adverse reaction is summarized in Table 1 below.

Table 1. Adverse Reactions Reported During the Field Study

Adverse Reaction	Miratаz 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	13 (11.3%)	2 (1.7%)
Hyperactivity	8 (7.0%)	1 (0.9%)
Disoriented state or ataxia	4 (3.5%)	2 (1.7%)
Lethargy/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%)
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.

** At Week 2, blood urea nitrogen (BUN) values were significantly higher in the Miratаz group compared to the vehicle control group ($p<0.10$). The BUN in the Miratаz group was 43.60 mg/dL (reference range 16-37 mg/dL) compared to 36.05 mg/dL in the vehicle control group.

Post study, follow-up was done in 199 cats (103 in the Miratаz (mirtazapine transdermal ointment) group and 96 in the vehicle control group). Following cessation of Miratаz, four cats were reported as 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 the litter box.

To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Dechra at (866) 933-2472.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at **http://www.fda.gov/reportanimalae**

INFORMATION FOR CAT OWNERS:
Upon discontinuation of Miratаz, it is important to monitor your cat's food intake. Your cat's food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days or if your cat stops eating for more than 48 hours, contact your veterinarian.

CLINICAL PHARMACOLOGY:
Mechanism of Action:
The exact mechanism by which mirtazapine induces weight gain has not been clearly elucidated but appears to be multifactorial.[1] Mirtazapine is an α2-adrenergic receptor antagonist nor-adrenergic and serotonergic antidepressant drug. Mirtazapine is known to be a potent antagonist of 5-HT2 and 5-HT3 serotonin receptors in the central nervous system (CNS), and a potent inhibitor of histamine H1 receptors. Because mirtazapine blocks 5-HT2 and 5-HT3 receptors, only 5-HT1A- mediated serotonergic transmission is enhanced. Inhibition of 5-HT2 receptors may account for the orexigenic effects of mirtazapine. Another hypothesis is that mirtazapine induced weight gain may be secondary to changes in leptin and the tumor necrosis factor α(TNF-α) cytokine system.[2] A study by Fernstorm (1995) demonstrated a reduction of the basal metabolic rate in patients treated with antidepressants in general.[3]

Pharmacokinetics:
In a crossover study in eight cats to determine the relative bioavailability of oral and transdermal 2% mirtazapine, the mean half-life (26.8 hours) with topical administration was over 2X longer than the mean half-life (10.1 hours) with oral administration.

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 2).

Steady state was achieved within 14 days. The median accumulation between first and 35th dose was 3.71X (based on AUC ratio) and 3.90X (based on C_{max} ratio).

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

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

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

EFFECTIVENESS:
The effectiveness of Miratаz (mirtazapine transdermal ointment) was demonstrated in a randomized, double-masked, vehicle-controlled, multi-site field study involving client-owned cats of various breeds.

Enrolled cats were ≥ 1 year of age and had existing documented medical history of ≥ 5% weight loss deemed clinically significant. The most common pre-existing conditions included renal insufficiency, vomiting, and hyperthyroidism. Some cats had more than one pre-existing condition. Cats were randomized to treatment groups in a 1:1 ratio of Miratаz to vehicle control. A total of 230 cats were enrolled and received either Miratаz (115 cats) or a vehicle control (115 cats) containing the same inert ingredients without mirtazapine. The cats were 2.8-24.6 years of age and weighed 2.1-9.2 kg. The dosage was a 1.5-inch ribbon (approximately 2 mg/cat) mirtazapine or vehicle ointment administered topically to the inner pinna of the cat's ear.

A total of 177 cats were determined to be eligible for the effectiveness analysis; 83 cats were in the Miratаz group and 94 cats were in the vehicle control group. The primary effectiveness endpoint was the mean percent change in body weight from Day 1 to the Week 2 Visit.

At Week 2, the mean percent increase in body weight from Day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference between the two groups was significant ($p<0.0001$) based on a two-sample t-test assuming equal variances. A 95% confidence interval on the mean percent change in body weight for the Miratаz group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0.

ANIMAL SAFETY:
The margin of safety of mirtazapine was evaluated in one laboratory study, a comprehensive review of six pilot studies (five laboratory and one clinical) utilizing the final market formulation, and one laboratory study that was not final market formulation.

Laboratory Safety Study:
In a 6-week laboratory safety study, 48 healthy cats aged 7-10 months were dosed topically with mirtazapine once daily at 0 mg/kg (vehicle control), 1.1 mg/kg (1.4 to 2.7X), 3.2 mg/kg (4.3-7.5X), and 5.3 mg/kg (7.1-12.2X) body weight. Four cats/sex/group in the 1.1 and 3.2 mg/kg groups were dosed topically to the inner pinna of the ear, alternating between right and left ears. Eight cats/sex/group in the 0 and 5.3 mg/kg groups were dosed topically to the inner pinna of the ear, splitting the dose between both ears. Four cats/sex/group in the 0 and 5.3 mg/kg groups were maintained and monitored during a 4-week recovery period.

6 Week Dosing Period
Application of mirtazapine and vehicle control was associated with ear flicking, head shaking, pulling away/flinching and infrequently with struggling/fractious behavior, and hypersalivation. Inner and outer pinna erythema, flaking, alopecia, and thickening were observed in all cats in all groups. Erythema, crusting, alopecia, and scabbing of the skin, mostly around the head and neck, was frequently observed in all groups and occasionally affected the tail, tarsi or carpi, likely due to spread of the ointment to these areas by self-grooming.

Mirtazapine administration resulted in increased vocalization, hyperactivity, attention-seeking behaviors, and tremors in all mirtazapine dose groups. Frank blood in the stool was infrequently observed in the vehicle control, 3.2, and 5.3 mg/kg groups. Polyuria was observed in all groups. Polydipsia was observed in one cat in the 5.3 mg/kg group. Three cats (one from each mirtazapine dose group) were isosthenuric. Eight cats developed cystitis with or without urethral obstruction throughout the study in all groups. One cat each from the vehicle control and 3.2 mg/kg group were euthanized early on Day 35 due to urethral obstruction.

Two cats from the 1.1 mg/kg group had either ventricular premature contractions (VPC) or tall R waves, and one cat from the 5.3 mg/kg group had both VPC and a right axis deviation.

Eosinophilia was noted sporadically in the vehicle control, 1.1, and 5.3 mg/kg groups. Mild elevations in ALT values were noted sporadically in vehicle control, 3.2, and 5.3 mg/kg groups. On Day 15, one cat in the 3.2 mg/kg group demonstrated a marked ALT elevation of 3397 U/L, with concurrent elevations in AST and GGT. By Day 42, the ALT declined to 109 U/L and the AST and GGT returned to within normal limits.

Gross pathology findings, confirmed with histopathology, were hyperplastic dermatitis (alopecia, hyperkeratosis, thickening, and ceruminous gland secretion) of the pinnae in all cats and findings consistent with cystitis (mucosal urinary bladder hemorrhage, mottled-dark red appearance, and irregular contour) in four male cats (two vehicle control, one 3.2 mg/kg and one 5.3 mg/kg). Additional histopathologic findings included pyelonephritis (two vehicle control and one 5.3 mg/kg), nephrocalcinosis (three vehicle control, one 1.1 mg/kg, three 3.2 mg/kg, and one 5.3 mg/kg), necrosis of the kidneys (one vehicle control and one 3.2 mg/kg), unilateral hypoplasia of the thyroid gland (two 5.3 mg/kg), and unilateral hypertrophy of the thyroid gland (one 5.3 mg/kg).

4 Week Recovery Period
Following a 4-week recovery period, ALT elevations resolved. Polyuria was reduced and only occurred in two cats in the 5.3 mg/kg group. Pinnal lesions (erythema and flaking) completely resolved in the vehicle control and improved in the 5.3 mg/kg groups. Ear thickening improved in both groups.

Pilot Safety Studies:
In six pilot studies (five laboratory and one clinical study) utilizing the final market formulation of Miratаz, and one laboratory study that utilized non-final market formulation, a total of 76 cats were administered mirtazapine. Five studies administered mirtazapine ointment topically (0.5-5.3 mg/kg), one study administered mirtazapine topically and orally (0.5 mg/kg), and one study administered mirtazapine orally (10.6 mg/cat).

The most common observations were ear pinnae reactions (erythema with or without blood and flaking), mild behavioral observations (vocalization and tremors), vomiting, and diarrhea.

One study reported six cats with blood in the stool. Two studies reported one cat each showing aggression. One study reported polyuria in one cat; another study reported stranguria and possible urinary tract infection in one cat. Two studies reported cardiac abnormalities, including sinus tachycardia not present at baseline, development of a grade 3/6 heart murmur, tall QRS complexes, and left or right axis deviation. One study reported one cat with ataxia. In the studies that administered mirtazapine orally, salivation and lip licking were frequently observed.

In the terminal study administering 5.3 mg/kg mirtazapine topically, histopathology showed chronic hyperplastic dermatitis at the application site.

STORAGE:
Store below 25°C (77°F). Multi-use tube. Discard within 30 days of first use.

HOW SUPPLIED:
Miratаz is supplied in a 5 gram aluminum tube.

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Approved by FDA under NADA # 141-481
NDC 17033-060-05

Manufactured for:
Dechra Veterinary Products
7015 College Boulevard, Suite 525
Overland Park, KS 66211 USA

US Patent 10,603,272

1411151 Rev. May 2020

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Mirataz®
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Manage weight loss in cats with Mirataz®

- Mirataz is the first and only FDA-approved transdermal medication for the management of weight loss in cats
- In a clinical study, Mirataz resulted in significant weight gain in cats in as little as 14 days following topical application of 2 mg per day[10]
- Mirataz gives you a practical way to manage your patient's weight loss without administration of oral medication and does not rely on the cat to eat to be medicated
- Formulated using proprietary Accusorb technology, Mirataz achieves measurable plasma concentrations of mirtazapine in cats[15]
- Mirataz was safe both locally and systemically in a clinical study[10]

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Important Safety Information

Mirataz® (mirtazapine transdermal ointment) is for topical use in cats only under veterinary supervision. Do not use in cats with a known hypersensitivity to mirtazapine or any of the excipients. Do not use in cats treated with monoamine oxidase inhibitors (MAOIs). Not for human use. Keep out of reach of children. Wear gloves when handling/applying, wash hands after and avoid contact between the treated cat and people or other animals for 2 hours following application. Use with caution in cats with hepatic and kidney disease. Cat's food intake should be monitored upon discontinuation. Safety has not been evaluated in cats less than 2 kg, less than six months of age or in breeding, pregnant or lactating cats. The most common adverse reactions observed during clinical trials were application site reactions, behavioral abnormalities (vocalization and hyperactivity) and vomiting. **For product label, including complete safety information, see pages 10-11.**

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01PG-MIR50248-1120

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