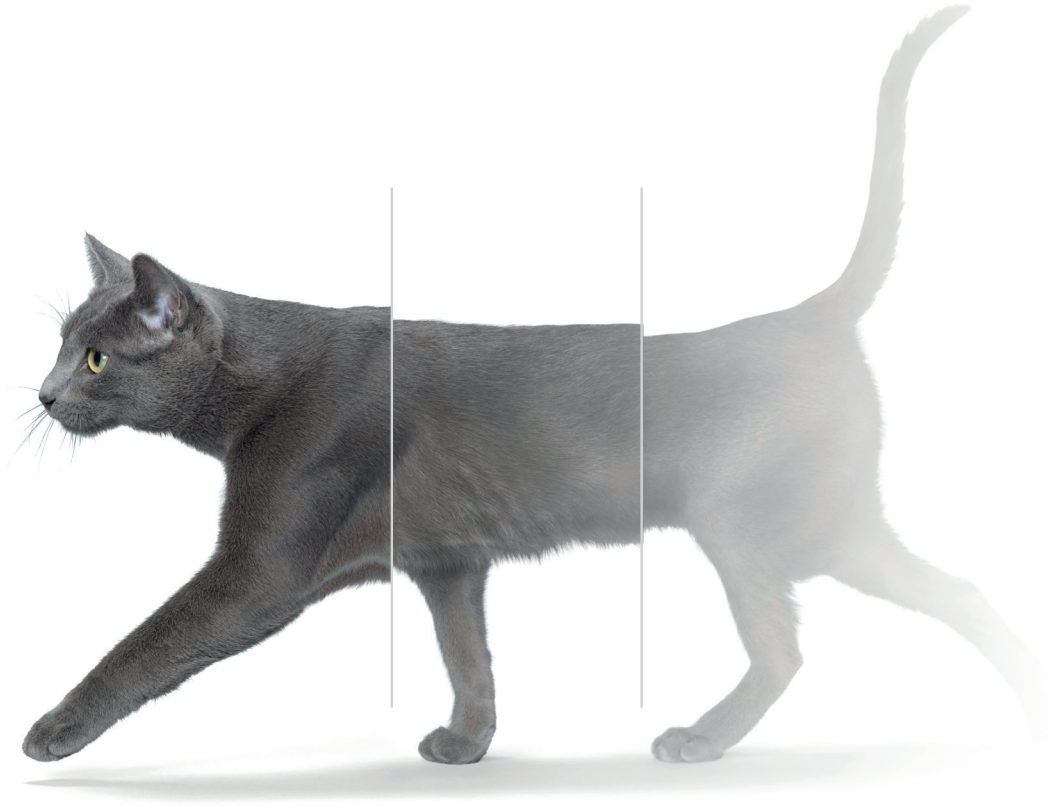
Dechra
Veterinary Products

Mirtazapine Pharmacokinetic Data: A Review

Produced by Dechra Veterinary Products, adapted from article originally written by Valentine S. Williams, DVM, MS, DACVS



Mirataz®

Take control with Mirataz

Introduction

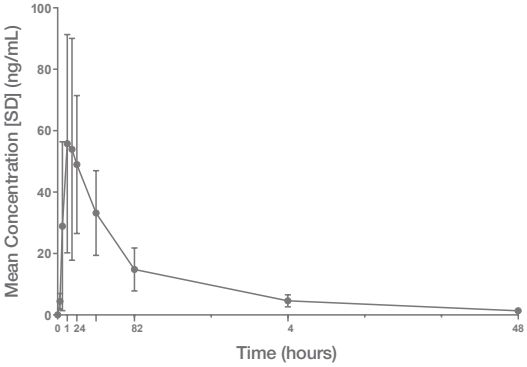
Mirataz is the first and only licensed veterinary medicine for body weight gain in cats experiencing poor appetite and weight loss, resulting from chronic medical conditions. It contains the active ingredient mirtazapine.

The use of mirtazapine in cats is not a new concept. Historically, mirtazapine has been administered orally in cats using human generic tablets, with dosing regimens based on extrapolation from human data with no species specific pharmacokinetics (PK) support[1]

Pharmacokinetics in Healthy Cats

PK of oral mirtazapine in cats has been studied and supports dosing at smaller doses and more frequent intervals[2-5] In a pooled population of healthy cats (n=22) receiving 1.88 mg of mirtazapine orally, the mean peak serum concentration (C_{max}) was 55.8 ng/ml. The time taken to reach mean peak serum concentration (T_{max}) was 1 hour, and the elimination half-life was 11.7 hours[2-4] (Figure 1).

Figure 1. Combined PK Curve in Healthy Cats Administered 1.88 mg of Mirtazapine Orally[a,b]

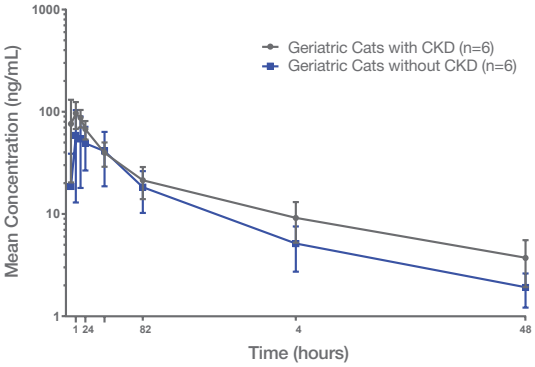


[a]Number of cats sampled: n=5 (0.25h); n=6 (1.5h, 2h); n=11 (0.5h, 8h, 48h); n=21 (4h); n=22 (1h, 24h). [b]Data reported with permission.[3-5]

Pharmacokinetics in Cats with Chronic Kidney Disease

In cats with chronic kidney disease (CKD) the half-life, C_{max}, and T_{max} of orally administered compounded mirtazapine were not significantly different than age-matched controls[3]. However, area under the curve (AUC) was significantly greater in cats with CKD indicating increased total drug exposure (Figure 2). Although not statistically significant, there was a trend towards a higher C_{max} in cats with CKD, which may account for the higher AUC. Additionally in this group of cats, renal clearance may be reduced, which may also contribute to higher drug exposure[3].

Figure 2. PK Curves in Cats with CKD and Age-Matched Controls Administered 1.88mg of Mirtazapine Orally[c]

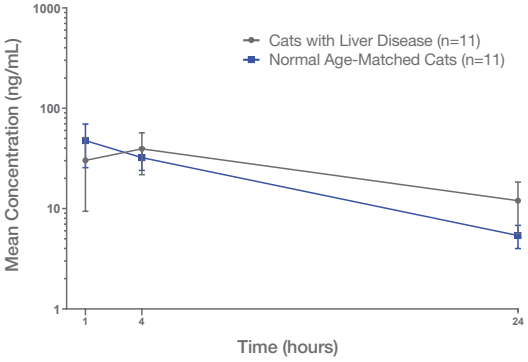


[c]Data first reported in Quimby JM *et al*. J Vet Intern Med., 2011;25:985-989.[3]

Pharmacokinetics in Cats with Liver Disease

In cats with liver disease that were administered mirtazapine orally, the half-life and T_{max} were prolonged compared to age-matched controls[4]. AUC was not significantly different (Figure 3). T_{max} prolongation is hypothesized to be due to poor intestinal perfusion and reduced absorption in cats with liver disease. Half-life is hypothesized to be prolonged due to reduced hepatic metabolism based on in vitro studies with hepatic microsomes[4].

Figure 3. PK Curves in Cats with Liver Disease and Age-Matched Controls Administered 1.88 mg of Mirtazapine Orally[d]

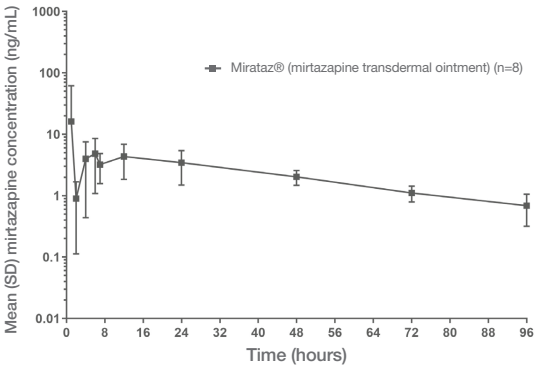


[d]Data first reported in Fitzpatrick RL *et al*. J Vet Intern Med., 2018;**32**:1951-1957.[4]

Pharmacokinetics of Mirataz

Transdermal mirtazapine has a number of PK differences following a single dose of 2 mg in healthy cats.
In comparison to oral mirtazapine, Mirataz has a lower C_{max}, lower AUC, and longer T_{max}[5] (Figure 4). 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.

Figure 4. PK Curve (+SD) after Single Topical Application of Mirataz (0.5 mg/kg)[e]



[e]Data first reported in Buhles W *et al*. J Vet Pharmacol Ther. 2018;**41**(5):644-651.[5]

Mirataz, as a transdermal, has been shown to be well tolerated when used according to the label in cats with suspected kidney disease, with no difference in incidence of overall adverse reactions or behavioural adverse reactions compared to cats without suspected kidney disease[6].

Summary

Mirataz is indicated for body weight gain in cats experiencing poor appetite and weight loss, resulting from chronic medical conditions. It is well tolerated and has been demonstrated to induce weight gain in as little as 14 days[7]. PK data, in comparison to oral dosing, suggests transdermal Mirataz has a lower maximum serum concentration and AUC.

Mirataz®
Mirtazapine transdermal ointment

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Miratаz 20 mg/g transdermal ointment for cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 0.1 g contains:

Active substance: Mirtazapine (as hemihydrate) 2 mg

Excipients: Butylhydroxytoluene (E321) 0.01 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal ointment.

Non-greasy, homogeneous, white to off-white ointment.

4. CLINICAL PARTICULARS

4.1 Target species

Cats

4.2 Indications for use, specifying the target species

For bodyweight gain in cats experiencing poor appetite and weight loss resulting from chronic medical conditions (see section 5.1).

4.3 Contraindications

Do not use in breeding, pregnant or lactating cats.

Do not use in animals less than 7.5 months of age or less than 2 kg body weight.

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

Do not use in cats treated with cyproheptadine, tramadol or monoamine oxidase inhibitors (MAOIs) or treated with an MAOI within 14 days prior to treatment with the veterinary medicinal product as there may be an increased risk of serotonin syndrome (see section 4.8).

4.4 Special warnings for each target species

The efficacy of the veterinary medicinal product has not been established in cats less than 3 years of age.

The efficacy and safety of the veterinary medicinal product has not been established in cats with severe renal disease and/or neoplasia.

Proper diagnosis and treatment of the underlying disease is key to managing weight loss, and treatment options are dependent on the severity of weight loss and underlying disease(s). The management of any chronic disease associated with weight loss should include providing appropriate nutrition and monitoring body weight and appetite.

The therapy with mirtazapine should not replace necessary diagnostics and/or treatment regimens needed to manage the underlying disease(s) causing unintended weight loss.

The efficacy of the product was only demonstrated with a 14-day administration corresponding to the current recommendations (see section 4.9). Repetition of the treatment has not been investigated and as such should only be done after benefit-risk balance assessment by the veterinarian.

The efficacy and safety of the veterinary medicinal product has not been established in cats weighing less than 2.1 kg or more than 7.0 kg (see also section 4.9).

4.5 Special precautions for use

Special precautions for use in animals

The veterinary medicinal product should not be applied on damaged skin. In the case of hepatic disease, elevated hepatic enzyme levels may be observed.

Kidney disease may cause reduced clearance of mirtazapine, which may result in higher drug exposure. In these special cases, biochemical hepatic and renal parameters should be regularly monitored during the treatment.

The effects of mirtazapine on glucose regulation have not been evaluated. In the case of use in cats with diabetes mellitus, glycaemia should be regularly monitored.

When used in hypovolemic cats, supportive treatment (fluid therapy) should be implemented.

Care should be taken that other animals in the household do not come in contact with the application site until it is dry.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

The product can be absorbed via the cutaneous or oral route and can cause drowsiness or sedation.

Avoid direct contact with the product. Avoid contact with the treated animal for the first 12 hours after each daily application and until the application site is dry. It is therefore recommended to treat the animal in the evening. Treated animals should not be allowed to sleep with owners, especially children and pregnant women during all the period of the treatment.

Impermeable disposable protective gloves should be provided at the point of sale with the product and must be worn when handling and administering the veterinary medicinal product.

Thoroughly wash hands immediately after administration of the veterinary medicinal product or in case of skin contact with the product or the treated cat.

Limited data are available on the reproductive toxicity of mirtazapine. Given that pregnant women are considered a more sensitive population, it is recommended that pregnant women or women trying to conceive should avoid handling the product and avoid contact with treated animals throughout the treatment period.

The product may be harmful after ingestion.

Do not leave the tube out of its child-proof container except during the application phase. Children must not be present when applying the treatment to the cat.

The tube must be placed in the child-proof container after application, which must be closed immediately.

Do not eat, drink or smoke while handling the veterinary medicinal product.

The veterinary medicinal product is a skin sensitiser. People with known hypersensitivity to mirtazapine should not handle the veterinary medicinal product.

This veterinary medicinal product may cause eye and skin irritation. Avoid hand to mouth and hand to eye contact until hands have been thoroughly washed. In the case of contact with eyes, rinse the eyes thoroughly with clean water. In the case of contact with the skin, wash thoroughly with soap and warm water. If skin or eye irritation occurs or in case of accidental ingestion, seek immediately medical advice and show the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

Application site reaction(s) (erythema, crust/scab, residue, scaling/dryness, flaking, head shaking, dermatitis or irritation, alopecia, and pruritus) and behavioural changes (increased vocalisation, hyperactivity, disoriented state or ataxia, lethargy/ weakness, attention seeking and aggression) occurred very commonly in safety and clinical studies.

Vomiting, polyuria associated with reduced urine specific gravity, elevated blood urea nitrogen (BUN) and dehydration were commonly observed in safety and clinical studies. Depending on the severity of vomiting, dehydration or behavioural changes, administration of the product may be discontinued according to the benefit-risk assessment of the veterinarian.

These adverse events, including local reactions, resolved at the end of treatment period with no specific treatment.

In rare occasions, hypersensitivity reactions can occur. In these cases, the treatment should be immediately withdrawn.

In case of oral ingestion, in addition to effects cited above (except local reactions), salivation and tremors may rarely occur.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Mirtazapine has been identified as potentially reprotoxic in rats and rabbits.

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.

Pregnancy and lactation: Do not use during pregnancy and lactation (see section 4.3).

Fertility: Do not use in breeding animals (see section 4.3).

4.8 Interaction with other medicinal products and other forms of interaction

Do not use in cats treated with cyproheptadine, tramadol or monoamine oxidase inhibitors (MAOIs) or treated with an MAOI within 14 days prior to treatment with the veterinary medicinal product as there may be an increased risk of serotonin syndrome (see section 4.3).

Mirtazapine may increase sedative properties of benzodiazepines and of other substances with sedative properties (antihistamines H1, opiates). The plasma concentrations of mirtazapine may be also increased when used concomitantly with ketoconazole or cimetidine.

4.9 Amounts to be administered and administration route

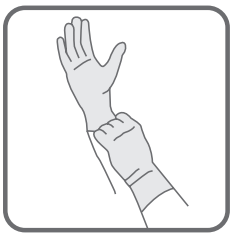
Transdermal use.

The veterinary medicinal product is applied topically to the inner pinna (inner surface of the ear) once daily for 14 days, at the dosage of 0.1 g ointment/cat (2 mg mirtazapine/cat). This corresponds to a 3.8 cm line of ointment (see below).

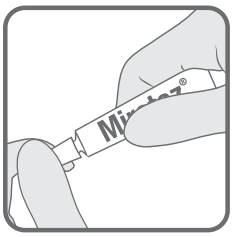
Alternate the daily application between the left and right ears. If desired, the inner surface of the cat's ear may be cleaned by wiping with a dry tissue or cloth immediately prior to the next scheduled dose. If a dose is missed, apply the veterinary medicinal product the following day and resume daily dosing.

The recommended fixed dose has been tested in cats weighing between 2.1 kg and 7.0 kg

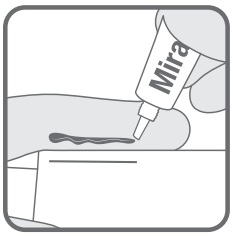
To apply the veterinary medicinal product:



Step 1: Put on impermeable gloves



Step 2: Twist cap on tube counter clockwise to open.



Step 3: Apply even pressure on tube and squeeze a 3.8 cm line of ointment onto your index finger using the measured line on the bottle or in this leaflet as a guide.

Step 4: Using your finger, gently rub ointment on inside surface of cat's ear (pinna) spreading it evenly over the surface. If contact with your skin occurs wash with soap and water.

The line below coincides with the appropriate length of ointment to be applied:

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

The known symptoms of a mirtazapine overdose of > 2.5 mg/kg in cats include: vocalization and behavioural changes, vomiting, ataxia, restlessness, and tremors. In case of an overdose, symptomatic/supportive treatment should be instituted if needed.

In the case of overdose, the same effects as those observed at the recommended therapeutic dose were noted but with a higher incidence.

Transient increased hepatic alanine transferase can be observed uncommonly. It is not associated with clinical signs.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic Group: Psychoanaleptics, antidepressants

ATCvet code: QN06AX11

5.1 Pharmacodynamic properties

Mirtazapine is an α2-adrenergic receptor antagonist nor-adrenergic and serotonergic antidepressant drug. The exact mechanism by which mirtazapine induces weight gain appears to be multifactorial. Mirtazapine is a potent antagonist of 5-HT2 and 5-HT3 receptors in the central nervous system (CNS), and a potent inhibitor of histamine H1 receptors. Inhibition of 5-HT2 and histamine H1 receptors may account for the orexigenic effects of the molecule. Mirtazapine-induced weight gain may be secondary to changes in leptin and the tumour necrosis factor (TNF).

The product has an expected positive effect on feed intake by stimulating the appetite but this effect was not measured in the pivotal field trial. The only effect tested under field practice was on bodyweight: client-owned cats presented with a weight loss ≥ 5%, deemed clinically significant by the investigator, gained a statistically significant ($p<0.0001$) amount of weight, after 14 days of product administration (3.39% weight gain or average of 130 grams) compared to those cats administered placebo (0.09% weight gain or average of 10 grams).

5.2 Pharmacokinetic particulars

In a crossover study conducted with the product at 0.5 mg/kg in eight cats to determine the relative bioavailability of oral and transdermal 2% mirtazapine, the mean terminal half-life (25.6 ± 5.5 hours) with topical administration was over 2X longer than the mean terminal half-life (8.63 ±3.9 hours) with oral administration. Bioavailability following topical administration was 34% (6.5 to 89%) compared to oral administration during the first 24 hours and 65% (40.1 to 128.0%) based on AUC0-∞. After a single topical administration, the mean peak plasma concentration of 21.5 ng/ml (± 43.5) is reached in Tmax mean of 15.9 hours (1-48 hours). The mean AUC0-24 was 100 ng*h/ml (± 51.7).

After administration of the product to 8 cats at a dose of 0.5 mg/kg once daily for 14 days, mean peak plasma concentration of 39.6 ng/ml (± 9.72) is reached in Tmax mean of 2.13 hours (1-4 hours). The mean terminal half-life of mirtazapine was 19.9 h (± 3.70) and the mean AUC0-24 was 400 ng*h/ml (±100).

In the target animal safety study, where cats received a higher dose (2.8 to 5.4 mg) than the label dose (2 mg) once daily for 42 days, 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 Cmax ratio).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 400

Macrogol 3350

Diethylene glycol monoethyl ether

Caprylocaproyl polyoxyglycerides

Oleyl alcohol

Butylhydroxytoluene (E321)

Dimethicone

Tapioca starch polymethylsilsesquioxane

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: 30 days.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

The tube must be stored in the child resistant bottle with cap and returned to the bottle and capped immediately after every use.

6.5 Nature and composition of immediate packaging

5 gram coated aluminium tube (coat: lacquer (internal)/ enamel (external) with a low-density polyethylene (LDPE) screw cap and crimp sealant.

Each plastic bottle with a child resistant cap contains 1 tube (5 g) .

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Aniserve GmbH
Geyerspergerstr. 27
80689 Munich
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/19/247/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10/12/2019

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

<{DD/MM/YYYY}>

<{DD month YYYY}>

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

References

1. Cahill, C. (2006) Mirtazapine as an Antiemetic. *Veterinary Forum*, 34-36
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7. Poole M., Quimby J., *et al*. (2019) A double blind, placebo-controlled, randomized study to evaluate the weight gain drug, mirtazapine transdermal ointment, in cats with unintended weight loss, *Journal of Veterinary Pharmacology and Therapeutics*, **42**(2) : 179-188

MIRATAZ: Mirataz contains Mirtazapine UK: POM-V **IE:** POM

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