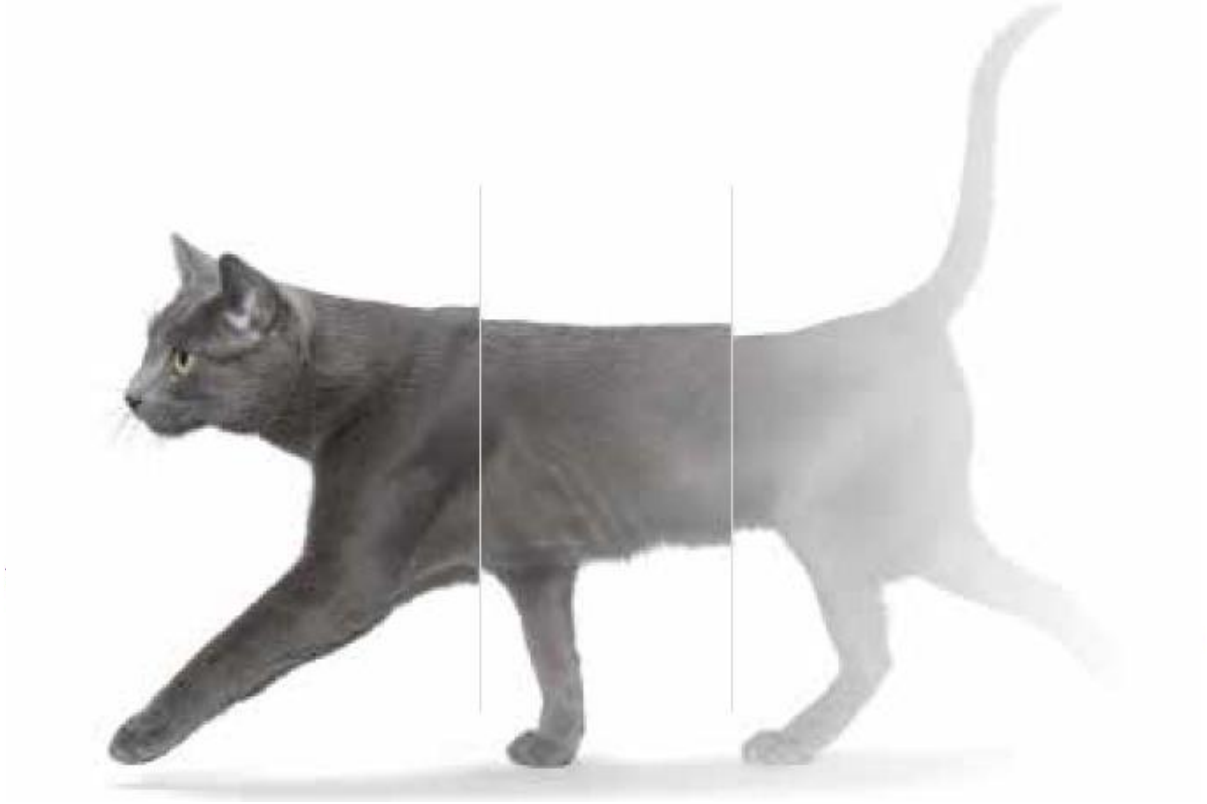
Reagieren statt Gewicht verlieren Mirataz®



Was ist Mirataz® ?

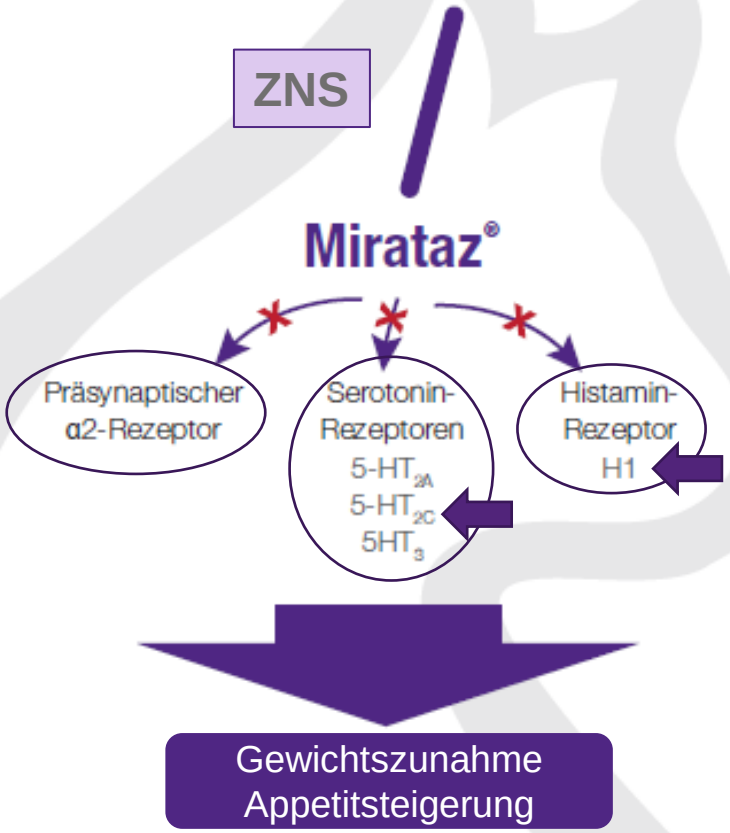
- Das **erste** und **einzige zugelassene Tierarzneimittel** zur **Gewichtszunahme bei Katzen** mit Appetitlosigkeit und Gewichtsverlust infolge chronischer Erkrankungen.

- **Salbe** (5g-Tube) zur Anwendung an der Ohrmuschel.

- Wirkstoff: **Mirtazapin (20 mg/g)**

Bisher:
Human zugelassene Tabletten

Wie wirkt Mirataz® - Mirtazapin ?



Antagonistische Bindung an **Rezeptoren** im **ZNS**, welche **an Appetit, Erbrechen** und **Übelkeit** beteiligt sind.

Mirtazapin = **serotonerges, noradrenerges** Antidepressivum
→ Erhöht Ausschüttung von **Noradrenalin** und **Serotonin**

Appetitsteigerung v.a. durch **antagonistische Bindung** an
→ **5-HT2** - Serotonin- Rezeptor (Appetitreduzierend) und
→ Histamin - **H1 Rezeptor** (hemmt Futteraufnahme)

Wirksamkeit Mirataz®

ORIGINAL ARTICLE

WILEY Journal of Veterinary Pharmacology and Therapeutics

A double-blind, placebo-controlled, randomized study to evaluate the weight gain drug, mirtazapine transdermal ointment, in cats with unintended weight loss

Melinda Poole[1] | Jessica M. Quimby[2] | Tianhua Hu[1] | Daizie Labelle[1] | William Buhles[1]

Abstract

Mirtazapine is classified as a weight gain drug in cats, and the purpose of this study was to evaluate its efficacy in cats experiencing unintended weight loss. This was a multi-center, double-blind, placebo-controlled, randomized clinical study in client-owned cats ≥1 year of age, weighing ≥2 kg, with a documented loss (≥5%) in body weight. Cats were treated once daily with either 2 mg/cat mirtazapine transdermal ointment (*n* = 83) or placebo (*n* = 94) (Per Protocol population) applied to the inner surface of the pinna for 14 ± 3 days. Physical examination, body weight, complete blood count, serum chemistry, and urinalysis were performed prior to treatment and on Day 14. Changes in body weight between the mirtazapine and placebo groups

Grunderkrankungen

Anwendungsgebiet für Mirataz® sehr breit!

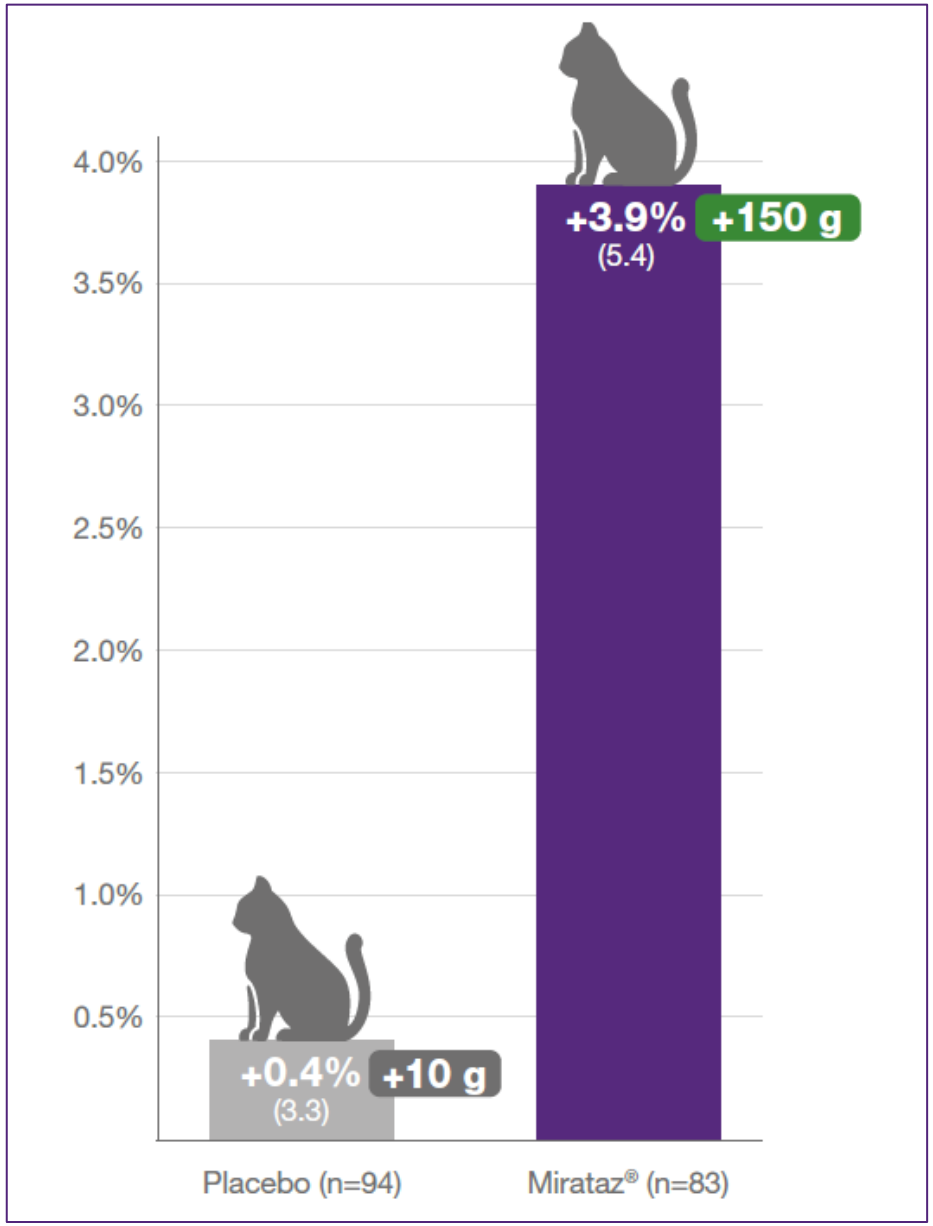
Table 3: Concomitant medications administered (occurring in >3% of cats in any treatment group [Sa population])[7]

Concomitant Medication Category	Mirtaz (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%)

Wirksamkeit Mirataz®

on Day 14. Changes in body weight between the mirtazapine and placebo groups were evaluated from Day 1 to Day 14 and compared using a two-sample *t* test. The mean percent change in body weight was +3.9% (standard deviation ±5.4%) in the mirtazapine group and +0.4% (±3.3%) in the placebo group ($p < 0.0001$). The most common adverse event was mild erythema at the application site in 17.4% of placebo and 10.4% of mirtazapine-treated cats. Application of mirtazapine transdermal oint-

Mirataz® bekämpft Appetitlosigkeit und bewirkt bei Katzen eine SIGNIFIKANTE GEWICHTSZUNAHME (BWG + 3,9%) in 14 Tagen



Wirksamkeit Mirataz®

Symptomatische Therapie ⇄ **Diagnose**

➡ **Verbessert** noch vor der Diagnose den **Allgemeinzustand**

➡ **Unterstützt chronisch kranke** Katzen

Nebenwirkungen Mirataz®

Table 1. Total incidence of adverse events (occurring in >5% of cats) [Sa population][1]

Adverse event	Mirtazapine (n = 115) n (%)	Placebo (n = 115) n (%)
Total Incidence	**70 (60.9%)**	**75 (65.2%)**
Vomiting	13 (11.3%)	15 (13.0%)
Vocalisation (including crying, meowing)	13 (11.3%)	2 (1.7%)
Application site erythema[a]	12 (10.4%)	20 (17.4%)
Hyperactivity (including pacing, restlessness, sleepnessless)	8 (7.0%)	1 (0.9%)
Haematuria	7 (6.1%)	1 (0.9%)
Diarrhoea or soft stool	6 (5.2%)	7 (6.1%)
Dehydration	6 (5.2%)	5 (4.3%)
Elevated BUN (without creatinine)	6 (5.2%)	0
Heart murmur	5 (4.3%)	7 (6.1%)
Lethargy (including depressed, sedation, weakness)	4 (3.5%)	9 (7.8%)
Anaemia	3 (2.6%)	8 (7.0%)
Application site residue	3 (2.6%)	8 (7.0%)
Application site crust/scab	3 (2.6%)	6 (5.2%)
Application site dermatitis or irritation[a]	1 (0.9%)	9 (7.8%)

[a]Application site dermatitis as defined by the clinical investigator and application site erythema as defined by reddening or discoloration not classified by the clinical investigator as dermatitis or irritation.

Keine signifikanten Unterschiede zwischen Mirataz® und Placebo!

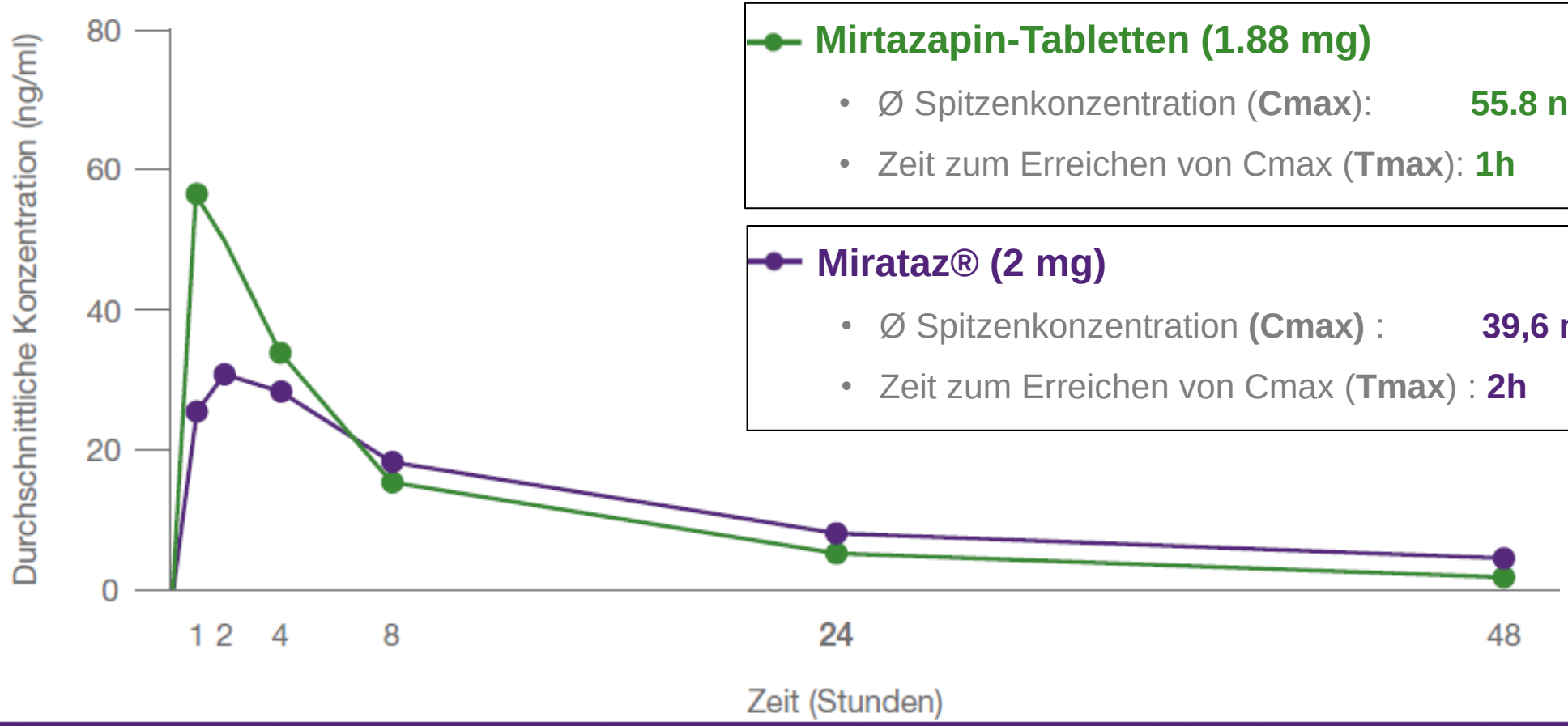
→ **Mirataz® sehr gut verträglich**

Reaktionen an der Applikationsstelle Ohr
Sehr häufig (1:10): Rötung, Verkrustung, Schuppen, Dermatitis, Juckreiz, Alopezie, Kopfschütteln

Verhaltensveränderungen
Sehr häufig (1:10): **Vokalisieren**, **Hyperaktivität**, Ataxie, Desorientierung, Aggression, Schwäche

Erbrechen, Polyurie
häufig (<10/100)

Pharmakokinetik (PK) Tablette vs. Salbe



Mirtazapin-Tabletten (1.88 mg)

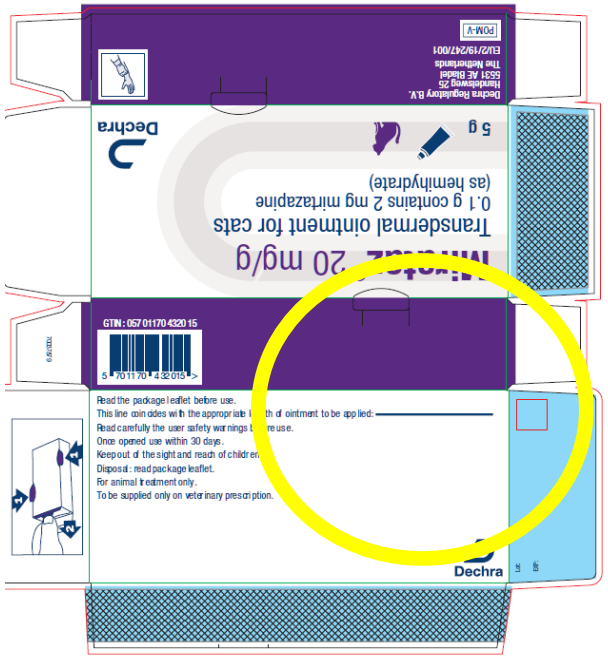
- Ø Spitzenkonzentration (**Cmax**): **55.8 ng/ml**
- Zeit zum Erreichen von Cmax (**Tmax**): **1h**

Mirataz® (2 mg)

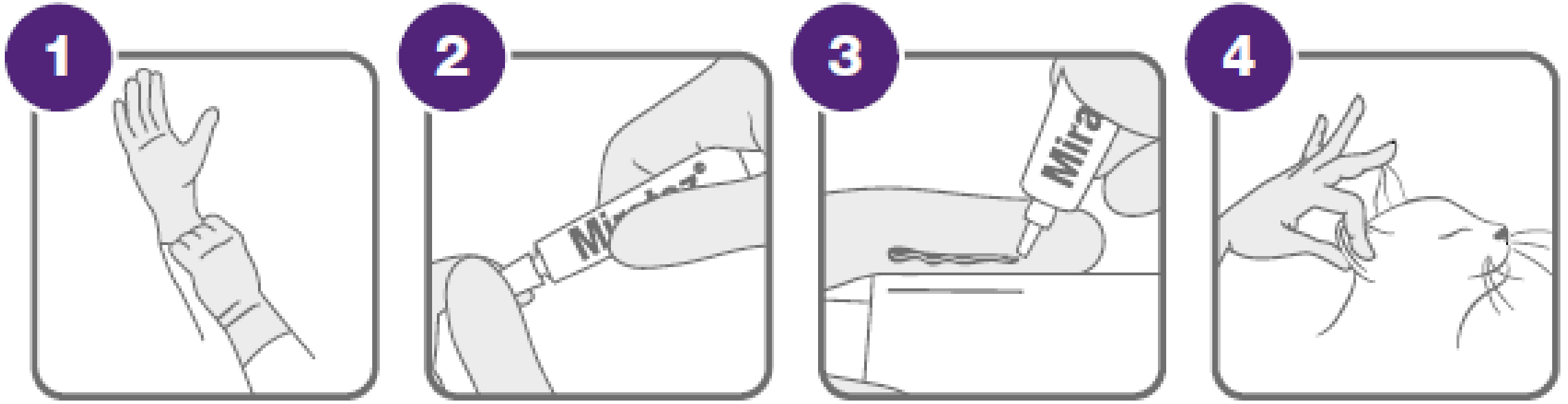
- Ø Spitzenkonzentration **(Cmax)** : **39,6 ng/ml**
- Zeit zum Erreichen von Cmax (**Tmax**) : **2h**

Anwendung/Dosierung

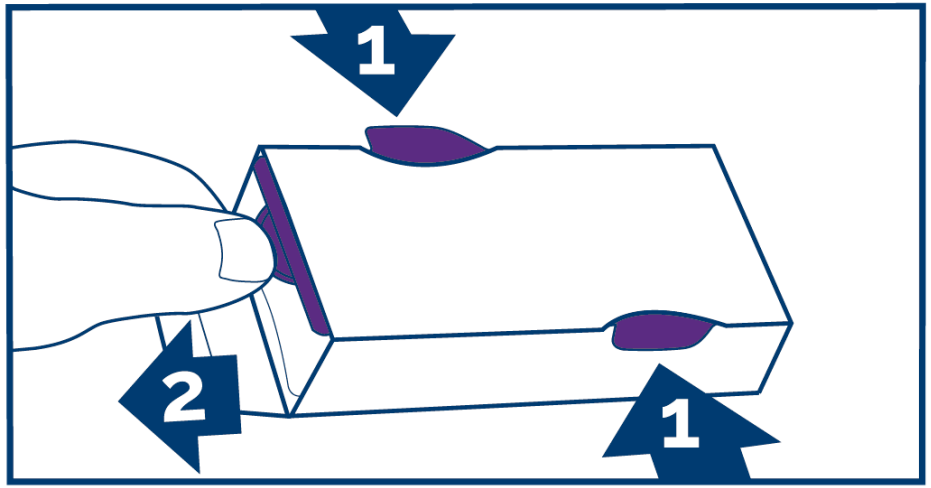
- Dosierung: **0,1g der Salbe/Katze (=2 mg Wirkstoff)** entspricht einem **Salbenstreifen von 3,8 cm** (siehe Linie auf Packung)
- Anwendung erfolgt **1x täglich über 14 Tage**
- Täglich **zwischen rechten** und **linken Ohr wechseln**
- **Handschuhe** tragen !
- Anwendung an der **Innenseite der Ohrmuschel**



Anwendung von Mirataz®



Kindersichere Verpackung



Vorsichtsmaßnahmen

Warum muss der Kontakt mit der Katze 12 Stunden nach Anwendung vermieden werden ?

Der direkte Kontakt mit dem Arzneimittel ist zu vermeiden. Der Kontakt mit dem behandelten Tier nach jeder täglichen Anwendung ist während der ersten 12 Stunden und bis zum Abtrocknen der Anwendungsstelle zu vermeiden. Daher wird empfohlen, das Tier abends zu behandeln. Behandelte Tiere sollten während der gesamten Dauer der Behandlung nicht bei den Tierhaltern, vor allem nicht bei Kindern und schwangeren Frauen, schlafen dürfen.

Mirataz®

1. Ist das **erste** und **einzige zugelassene Tierarzneimittel** mit dem **Wirkstoff Mirtazapin**.
2. Führt in nur 14 Tagen zu einer **signifikanten Gewichtszunahme**.
3. Ist als Salbe **einfach anzuwenden**.
4. Kann **bei vielen Grunderkrankungen** eingesetzt werden.
5. Kann den **Allgemeinzustand noch vor der Diagnose bessern.**

Reagieren statt Gewicht verlieren Mirataz®

→ **fachfrage@dechra.com**

→ **www.dechra.de/mirataz**

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JOURNAL OF
Veterinary Pharmacology and Therapeutics

PHARMACOKINETIC REPORT | Open Access

Single and multiple dose pharmacokinetics of a novel mirtazapine transdermal ointment in cats

William Buhles, Jessica M. Quimby, Daizie Labelle, Valentine S. Williams

First published: 13 July 2018 | https://doi.org/10.1111/jvp.12691 | Citations: 5

Abstract

Single and multiple dose pharmacokinetics (PK) of mirtazapine transdermal ointment applied to the inner ear pinna of cats were assessed. Study 1 was a randomized, cross-over single dose study (*n* = 8). Cats were treated once with 0.5 mg/kg of mirtazapine transdermal ointment applied topically to the inner ear pinna (treatment) or administered orally (control) and then crossed over after washout. Plasma was collected predose and at specified intervals over 96 hr following dosing. Study 2 was a multiple dose study (*n* = 8). Cats were treated daily for 14 days with 0.5 mg/kg of mirtazapine transdermal ointment applied topically to the inner pinna. Plasma was collected on Day 13 predose and at specified intervals over 96 hr following the final dose. In Study 1, single transdermal administration of mirtazapine resulted in mean T_{max} = 15.9 hr, C_{max} = 21.5 ng/mL, $AUC_{0\text{-}24}$ = 100 ng*hr/mL, $AUC_{0\text{-}\infty}$ = 260 ng*hr/mL and calculated half-life = 26.8 hr. Single oral administration of mirtazapine resulted in mean T_{max} = 1.1 hr, C_{max} = 83.1 ng/mL, $AUC_{0\text{-}24}$ = 377 ng*hr/mL, $AUC_{0\text{-}\infty}$ = 434 ng*hr/mL and calculated half-life = 10.1 hr. Mean relative bioavailability (*F*) of transdermal to oral dosing was 64.9%. In Study 2, daily application of mirtazapine for 14 days resulted in mean T_{max} = 2.1 hr, C_{max} = 39.6 ng/mL, $AUC_{0\text{-}24}$ = 400 ng*hr/mL, $AUC_{0\text{-}\infty}$ = 647 ng*hr/mL and calculated half-life = 20.7 hr. Single and repeat topical doses of a novel mirtazapine transdermal ointment achieve measurable plasma concentrations in cats.

Clinical Trial > J Vet Pharmacol Ther. 2011 Aug;34(4):388-96.
doi: 10.1111/j.1365-2885.2010.01244.x. Epub 2010 Oct 24.

Studies on the pharmacokinetics and pharmacodynamics of mirtazapine in healthy young cats

J M Quimby [1], D L Gustafson, B J Samber, K F Lunn

Abstract

Mirtazapine pharmacokinetics was studied in 10 healthy cats. Blood was collected before, and at intervals up to 72 h after, oral dose of 3.75 mg (high dose: HD) or 1.88 mg (low dose: LD) of mirtazapine. Liquid chromatography coupled to tandem mass spectrometry was used to measure mirtazapine, 8-hydroxymirtazapine and glucuronide metabolite concentrations. Noncompartmental pharmacokinetic modeling was performed. Median half-life was 15.9 h (HD) and 9.2 h (LD). Using Mann-Whitney analysis, a statistically significant difference between the elimination half-life, clearance, area under the curve (AUC) per dose, and AUC(∞) /dose of the groups was found. Mirtazapine does not appear to display linear pharmacokinetics in cats. There was no significant difference in glucuronidated metabolite concentration between groups. Pharmacodynamics was studied in 14 healthy cats administered placebo, LD and HD mirtazapine orally once in a crossover, blinded trial. In comparison with placebo, cats ingested significantly more food when mirtazapine was administered. No difference in food ingestion was seen between HD and LD, but significantly more behavior changes were seen with the HD. Limited serum sampling during the pharmacodynamic study revealed drug exposure comparable with the pharmacokinetic study, but no correlation between exposure and food consumed. Mirtazapine (LD) was administered daily for 6 days with no drug accumulation detected.

J Vet Intern Med. 2018 Nov;32(6):1951-1957. doi: 10.1111/jvim.15237. Epub 2018 Oct 11.

In vivo and in vitro assessment of mirtazapine pharmacokinetics in cats with liver disease

Rikki L Fitzpatrick [1], Jessica M Quimby [1], Kellyi K Benson [1], Dominique Ramirez [1], Liberty G Sieberg [1], Luke A Wittenburg [1], Daniel L Gustafson [1]

Abstract

Background: Liver disease (LD) prolongs mirtazapine half-life in humans, but it is unknown if this occurs in cats with LD and healthy cats.

Hypothesis/objectives: To determine pharmacokinetics of administered orally mirtazapine in vivo and in vitro (liver microsomes) in cats with LD and healthy cats.

Animals: Eleven LD and 11 age-matched control cats.

Methods: Case-control study. Serum was obtained 1 and 4 hours (22 cats) and 24 hours (14 cats) after oral administration of 1.88 mg mirtazapine. Mirtazapine concentrations were measured by liquid chromatography with tandem mass spectrometry. Drug exposure and half-life were predicted using limited sampling modeling and estimated using noncompartmental methods. in vitro mirtazapine pharmacokinetics were assessed using liver microsomes from 3 LD cats and 4 cats without LD.

Results: There was a significant difference in time to maximum serum concentration between LD cats and control cats (median [range]: 4 [1-4] hours versus 1 [1-4] hours; P = .03). The calculated half-life of LD cats was significantly prolonged compared to controls (median [range]: 13.8 [7.9-61.4] hours versus 7.4 [6.7-9.1] hours; P < .002). Mirtazapine half-life was correlated with ALT (P = .002; r = .76), ALP (P < .0001; r = .89), and total bilirubin (P = .0008; r = .81). The rate of loss of mirtazapine was significantly different between microsomes of LD cats (-0.0022 min^{-1} , CI: -0.0050 to 0.00054 min^{-1}) and cats without LD (0.01849 min^{-1} , CI: -0.025 to -0.012 min^{-1} ; P = .002).

Conclusions and clinical importance: Cats with LD might require less frequent administration of mirtazapine than normal cats.

Keywords: appetite stimulant; feline; hepatic; microsomes.

J Vet Intern Med. Sep-Oct 2011;25(5):985-9. doi: 10.1111/j.1939-1676.2011.00780.x.
Epub 2011 Aug 30.

The pharmacokinetics of mirtazapine in cats with chronic kidney disease and in age-matched control cats

J M Quimby [1], D L Gustafson, K F Lunn

Abstract

Background: Cats with chronic kidney disease (CKD) often experience inappetence, and may benefit from administration of mirtazapine, an appetite stimulant. The pharmacokinetics of mirtazapine in CKD cats is unknown.

Hypothesis: CKD delays the clearance/bioavailability (CL/F) of mirtazapine.

Animals: Six CKD cats and 6 age-matched controls (AMC) were enrolled. Two CKD cats each from International Renal Interest Society (IRIS) stage II, III and IV were included.

Methods: Blood samples were collected before and 0.5, 1, 1.5, 2, 4, 8, 24, and 48 hours after a single PO dose of 1.88 mg of mirtazapine. Mirtazapine concentrations were measured by liquid chromatography coupled to tandem mass spectrometry. Non-compartmental pharmacokinetic modeling was performed.

Results: Mean age was 11 years (CKD cats) and 10.8 years (AMC cats). Mean serum creatinine concentration ± standard deviation (SD) was 3.8 ± 1.6 mg/dL (CKD) and 1.3 ± 0.4 mg/dL (AMC). Mean half-life ± SD was 15.2 ± 4.2 hours (CKD) and 12.1 ± 1.1 hours (AMC). Mean area under the curve (AUC) ± SD was 770.6 ± 225.5 ng/mL•hr (CKD) and 555.5 ± 175.4 ng/mL•hr (AMC). Mean CL/F ± SD was 0.6 ± 0.1 L/hr/kg (CKD) and 0.8 ± 0.16 L/hr/kg (AMC). A Mann-Whitney test indicated statistically significant differences in AUC ($P = 0.01$) and CL/F ($P = 0.04$) between groups. Calculated accumulation factor for 48-hour dosing in CKD cats was 1.15.

Conclusion: CKD may delay the CL/F of mirtazapine. A single low dose of mirtazapine resulted in a half-life compatible with a 48-hour dosing interval in CKD cats.