

Feline Hyperthyroidism Technical Bulletin



Vidalta[®] (Carbimazole 10mg or 15mg)
Once-Daily Oral Tablets for Cats

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1 Introduction

Feline hyperthyroidism is the most common endocrinopathy diagnosed in domestic cats and is one of the most frequently diagnosed disorders in small animal practice¹, affecting approximately 1 in 300 cats in the UK², with a prevalence of 2% in cats presented to teaching hospitals in the USA³.

Management options include radioactive iodine therapy(¹³¹I), thyroidectomy, medical management with anti-thyroid drugs, such as carbimazole, or dietary management with a restricted iodine food.

Vidalta[®] 10mg and 15mg tablets are a novel controlled-release formulation of carbimazole, allowing once daily medical treatment of feline hyperthyroidism. Traditional oral treatment has relied on conventional carbimazole tablets for use in humans (NeoMercazole[®] 5mg) to be administered twice or three times daily leading to poor owner compliance and treatment failure.

Vidalta's once-daily controlled-release formulation improves owner compliance and satisfaction in treating feline hyperthyroidism.

2 Feline Hyperthyroidism

Feline hyperthyroidism is a multi-systemic disorder resulting from excessive levels of the circulating thyroxine (T4) and triiodothyronine (T3). Ninety-nine per cent of cases result from benign nodular hyperplasia, adenomatous hyperplasia or adenoma with both glands affected in 70-75% of cats. Only 1-3% of cases are caused by mild to moderately malignant thyroid carcinoma²; as such, the disease carries a favorable prognosis with effective therapy⁴.

Although the incidence of feline hyperthyroidism has increased steadily since the early 1980's, the cause is still unknown. A number of theories have been proposed including:

- Diet – high levels of iodine and goitrogenic compounds, such as phthalates
- Environmental factors– regular exposure to pesticides and fertilizers
- Genetic mutation
- Abnormal immune responses
- Abnormal hormonal responses

2.1 Clinical Findings

Hyperthyroidism is seen mainly in middle-aged to older cats, with a mean age of 12-13 years. There is no sex or breed predilection, however some studies suggest that Siamese and Himalayan cats may have a decreased risk.

Hyperthyroidism is a progressive disorder with a slow onset, becoming more clinically obvious with time. Many cats show clinical signs for 6-12 months prior to being presented to their veterinarian. Cat owners may think early signs are nothing more than signs of 'good health' (i.e. an increased appetite and high levels of activity) or the normal signs of aging (i.e. the gradual loss of coat and body condition).

Thyroid hormones have a wide variety of actions in many different body systems; many organs are involved and a variety of clinical signs can be seen. Clinical signs are also dependent on the duration of the condition and the presence of concurrent disease.

Clinical manifestations are variable and may include:

- Weight loss
- Polyphagia
- Tachycardia
- Systemic hypertension
- Polyuria/Polydipsia
- Hyperactivity
- Diarrhea
- Vomiting
- Ill-kempt coat
- Respiratory signs
- Lethargy
- Weakness
- Decreased appetite

Less commonly observed signs include: tremors/seizure, heat intolerance, haematuria, and neck ventroflexion.

2.2 Diagnosis²

Physical examination usually reveals a poor body condition, an ill-kempt coat and a palpable thyroid nodule on either side of the trachea (80-90% of cases). Affected cats generally have tachycardia (48%), a systolic murmur (41%), a gallop rhythm (12%) or ectopic beats. Hyperthyroid cats are often agitated, difficult to examine and become easily stressed.

Clinical pathology examination may reveal the following:

- Raised liver enzymes
 - ▶ ALT
 - ▶ ALP
- Azotemia
- Hypophosphatemia
- Hyperglycemia
- Hypokalemia
- Raised CK

Hematological testing may reveal:

- Erythrocytosis
- Macrocytosis
- Mild anaemia (severe disease)
- Mature neutrophilia
- Lymphopenia
- Lymphocytosis
- Eosinopenia or eosinophilia

It is important to consider all possible differential diagnosis and to look for evidence of multiple interacting diseases when investigating a cat for suspected hyperthyroidism. Important differential diagnoses include:

- Diabetes mellitus
- Renal disease
- Malassimilation syndrome
 - ▶ Inflammatory bowel disease
 - ▶ Early intestinal lymphoma
 - ▶ Pancreatitis
 - ▶ Exocrine pancreatic insufficiency
- Acromegaly
- Hyperadrenocorticism.

A definitive diagnosis of hyperthyroidism is based on detecting elevated serum concentrations of total T4 (tT4), and sometimes T3.

Some cats with hyperthyroidism may have a normal tT4 concentration as a result of early or mild hyperthyroidism, daily variations in tT4 concentrations or concurrent systemic illness causing a reduction in tT4 (euthyroid sick syndrome).

If a cat is suspected to have hyperthyroidism despite a normal to high tT4 concentration, other investigatory options could be considered:

- Retest the tT4 at a later stage (few weeks)
- Assessing free T4 (by equilibrium dialysis)
- T3 suppression test
- TRH stimulation test
- TSH response test
- Trial course of anti-thyroid medication for 30 days
- Nuclear isotope scanning

2.3 Treatment

The therapy for feline hyperthyroidism is directed at controlling the excessive production of thyroid hormones. Four options for therapy currently exist in New Zealand:

1. Anti-thyroid drug administration
 - a. Oral carbimazole
 - b. Topical thiamazole (methimazole)
2. Surgical thyroidectomy
3. Radioactive iodine treatment
4. Restricted iodine dietary management

The choice of treatment should be based on the circumstances of each individual cat and its owner, taking the following factors into consideration:

- Animal
 - ▶ Concurrent illness e.g. renal insufficiency, hypertension, cardiomyopathy
 - ▶ Temperament
 - ▶ General anesthetic risk
 - ▶ Dietary intolerances
 - ▶ Indoor versus outdoor (access to other food)
 - ▶ Tolerance of anti-thyroid medication

- Owner
 - ▶ Compliance
 - Ability to administer topical or oral medication
 - Ability to feed an exclusive diet
 - ▶ Lifestyle
 - ▶ Cost of treatment
- Environmental
 - ▶ Multi-cat household
 - ▶ Children
- Other
 - ▶ Availability of ¹³¹I treatment

2.3.1 Anti-thyroid drug administration

The class of anti-thyroid medication most commonly used to medically treat cats with hyperthyroidism is the mercaptoimidazoles (carbimazole and thiamazole [methimazole]). Thiamazole, the active metabolite of carbimazole, inhibits thyroid hormone production and therefore cessation of treatment with carbimazole will result in a rapid (within 48 hours) return to pre-treatment thyroid levels.

For most cats, carbimazole and thiamazole are generally safe and effective treatments for hyperthyroidism. Adverse effects are not uncommon and are usually mild and reversible. Poor appetite, vomiting and lethargy are the most likely side effects and often resolve after the first few weeks of treatment and/or by temporarily reducing the dose of the treatment. More serious problems, including leukopenia, thrombocytopenia, liver disorders or skin irritation are rare, but if they do occur, an alternative treatment must be used.

Anti-thyroid drugs can be used for lifelong management of feline hyperthyroidism or 'stabilising' a patient prior to ¹³¹I treatment or surgical thyroidectomy.

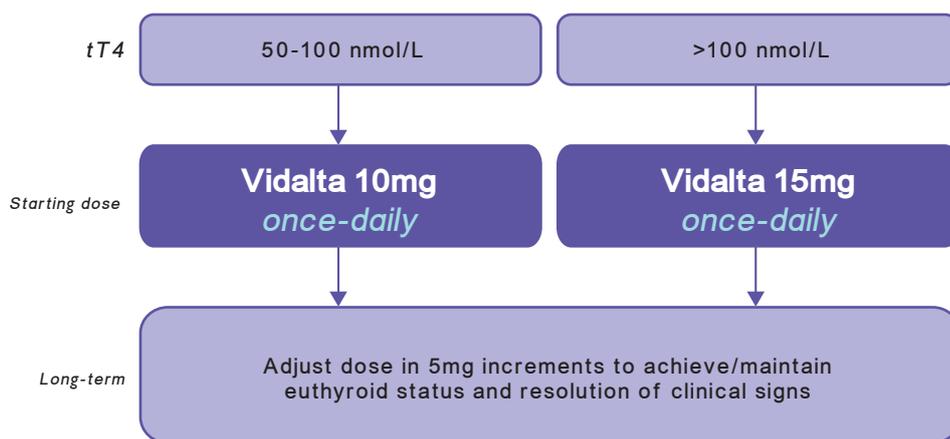
2.3.1.1 Once-daily oral carbimazole – Vidalta 10mg and Vidalta 15mg

The starting dose is a **single daily** oral administration of one tablet of Vidalta 15mg per cat. Consideration should be given to a starting dose of Vidalta 10mg daily where the tT4 concentration is only mildly increased, e.g. between 50 nmol/L and 100 nmol/L. With the recommended starting dose of one Vidalta 15mg once-daily, tT4 may decrease to within euthyroid range (tT4 < 50 nmol/L) shortly after

treatment initiation. A dose adjustment may be required as early as 10 days after commencing treatment. Dose adjustment should also be performed 3, 5 and 8 weeks after initiation of treatment, depending on both clinical and hormonal responses to treatment.

Using Vidalta

Suggested treatment protocol



Follow-up visits every 3 to 6 months are recommended. The dose should be adjusted individually based on clinical signs and tT4. It is advisable to check tT4 10-14 days after dose adjustment. The therapeutic dose of Vidalta ranges between 10mg (one 10mg tablet) and 25mg (one 10mg and one 15mg tablet) once-daily. Some cats require doses less than 10mg carbimazole daily. Every other day dosing with Vidalta 10mg or Vidalta 15mg may be sufficient to control the disease. Dose increases should not be made in increments of greater than 5mg. Doses above 20mg have only been trialled in a small number of cats and should be used with caution.

2.3.1.2 Once-daily topical thiamazole (methimazole)

Once-daily topical application of a transdermal lipophilic formulation of thiamazole (methimazole) to the pinnae of hyperthyroid cats has been shown to be as safe and effective as conventional twice-daily oral carbimazole (NeoMercazole 5mg) treatment.⁵ Disadvantages of transcutaneous drug delivery may include cutaneous irritation and potentially increased inadvertent drug exposure to clients or other animals.⁵

2.3.2 Surgical thyroidectomy

Surgical thyroidectomy is usually a highly effective treatment for feline hyperthyroidism. Unfortunately general anesthetic risk and surgical complications can result in significant morbidity and mortality. Greater than 70% of cats with hyperthyroidism will have bilateral thyroid gland involvement. In these cats, removal of both lobes is necessary for a successful outcome.

Post-operative complications include hypoparathyroidism (with resulting life-threatening hypocalcaemia), Horner's syndrome, laryngeal paralysis and persistent hypothyroidism (requiring thyroid hormone replacement treatment especially if concurrent renal insufficiency is present).

2.3.3 Radioactive iodine treatment(¹³¹I)

Although ¹³¹I treatment is deemed to be a safe and effective cure for feline hyperthyroidism, a small percentage of cats may become permanently hypothyroid and require life-long supplementation with oral levothyroxine sodium treatment. The hypothyroid state is of particular importance in cats that develop azotemia, as their expected lifespan may be significantly reduced without thyroid hormone replacement therapy.

2.3.4 Restricted iodine dietary management

Recent studies have indicated that a diet with restricted dietary iodine ($\leq 0.35\text{ppm}$) may provide a further option for management of feline hyperthyroidism.^{6,7}

Hyperthyroid cats fed this diet should not ingest iodine from other food sources (e.g. treats, another pet's food) as this can compromise the effectiveness of low-iodine nutrition.⁸

The long-term consequences of feeding a restricted iodine diet to hyperthyroid cats are not known, especially in normal cats in the household that are also fed this diet. Without adequate iodine to produce thyroid hormone, circulating T4 and T3 fall, which give rise to high serum levels of thyroid stimulating hormone (TSH). The high TSH acts on the thyroid gland to stimulate cellular growth and proliferation and induce thyroid hyperplasia and goiter (i.e. hyperthyroidism). A restricted iodine diet should therefore *not* be fed to euthyroid (normal) cats; this can be an issue in households with multiple cats.⁹

3 Pharmacokinetic Studies of Vidalta

The pharmacokinetics of carbimazole were investigated in clinically healthy male and female European shorthair cats following oral administration of a novel controlled-release tablet formulation (Vidalta 15mg). This included pharmacokinetic profiles following single and repeated oral administration, evaluation of relative and absolute bioavailability and the influence of food intake on the pharmacokinetics.⁷

3.1 Comparative pharmacokinetics of conventional and controlled-release (Vidalta® 15mg) carbimazole oral tablet formulations in healthy cats¹⁰

Once-daily administration of Vidalta provides prolonged thiamazole concentrations over 24 hours compared to conventional carbimazole tablets which have to be administered twice-daily.

Method

The pharmacokinetics of thiamazole was compared in 5 cats (2 female, 3 male, aged 3 ± 1.0 years, weighing 3.9 ± 0.5 kg) administered a single dose of carbimazole as a conventional (NeoMercazole 5mg) or controlled-release (Vidalta 15mg) tablet formulation. Cats were fasted overnight prior to the days of treatment and fed 4 hours after treatment was administered. Four days elapsed between treatments.

Results

The plasma concentrations of thiamazole vs. time profiles are shown in Figure 1. The pharmacokinetic parameters calculated are summarized in Table 1. The C_{\max} of the two different tablet formulations was comparable. T_{\max} was later for Vidalta 15mg compared with conventional carbimazole tablets. In most of the cats, the time for plasma thiamazole concentrations to return to pre-treatment value was longer than 24 hours following administration of Vidalta 15mg.

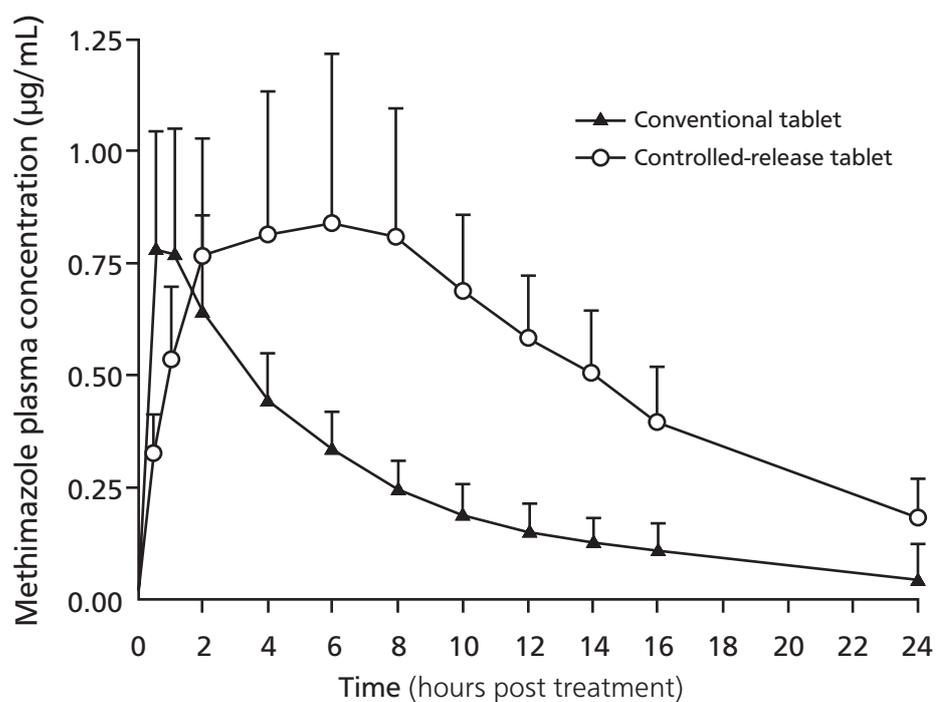


Fig 1. Plasma concentrations of methimazole (mean \pm SD) in cats ($n = 5$) following single oral administration of carbimazole as a controlled-release (15mg) and conventional (5mg) tablet.

Table 1: Pharmacokinetics of thiamazole in cats ($n = 5$) following a single oral administration of carbimazole as a controlled-release (Vidalta 15mg) or conventional (NeoMercazole 5mg) tablet

Parameter	Vidalta 15mg	Conventional tablet
Dose (mg/kg)	3.9 \pm 0.6	1.3 \pm 0.2
C_{max} ($\mu\text{g/mL}$)	0.99 \pm 0.29	0.80 \pm 0.27
t_{max} (h)	6 (2-10)	0.5 (0.5-1)
$t_{baseline}$ (h)	$\geq 24^*$	22 \pm 4
AUC ($\mu\text{g}\cdot\text{h/mL}$)	12.90 \pm 2.84	5.49 \pm 1.86
Relative bioavailability F (%)	83 \pm 21 [†]	-

Values are arithmetic mean \pm SD, except for t_{max} [median (range)].

*could not be determined in 4 out of 5 cats; [†]95% confidence interval (56-109%).

3.2 Bioavailability of thiamazole after oral administration of Vidalta 15mg¹⁰

Excellent bioavailability following Vidalta administration.

Method

The pharmacokinetics of thiamazole, including the absolute bioavailability, were determined in 7 cats (3 female, 4 male, aged 3.6 ± 1.8 years, weighing 4.5 ± 0.6 kg) following a single oral administration of Vidalta 15mg tablet or intravenous administration of an equimolar amount of thiamazole (1mL of a solution titrated 9.2g/L). A two-period crossover design with a washout of 4 days was used. Cats were fasted overnight prior treatment and were then fed within 2 hours after treatment.

Results

The plasma concentrations of thiamazole vs. time profiles are shown in Figure 2. The pharmacokinetic parameters calculated are summarized in Table 2. Following a single oral administration of the Vidalta 15mg tablet, the apparent half-life was longer (9.0 h) than the elimination half-life of intravenous administration of thiamazole (3.6 h). The absolute bioavailability following oral administration of the Vidalta 15mg tablet was $88 \pm 11\%$ (mean \pm SD).

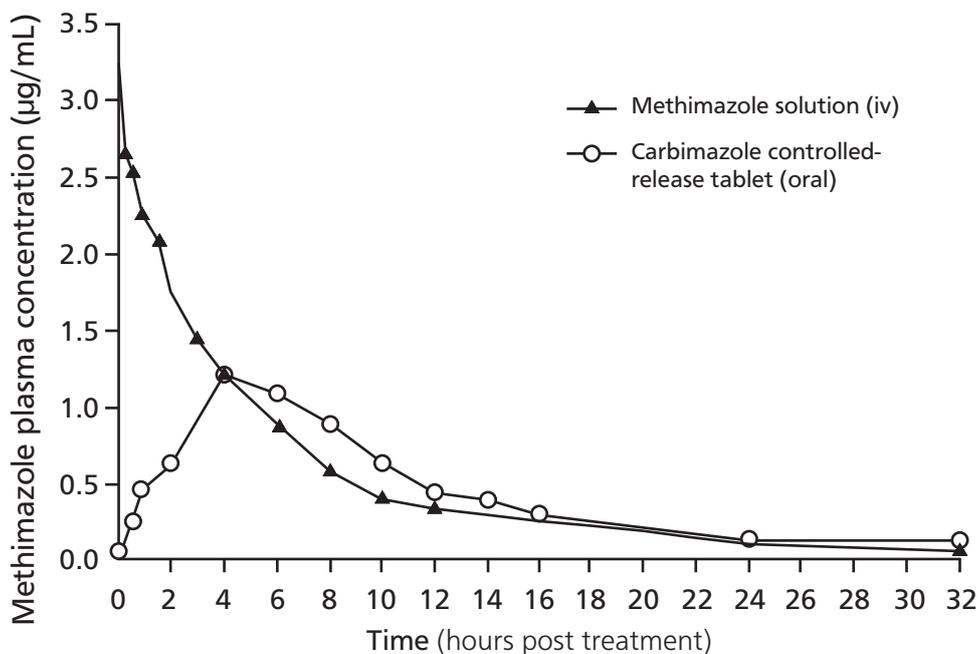


Fig 2. Plasma concentrations of methimazole (mean \pm SD) in cats ($n = 7$) following a single oral administration of carbimazole as a controlled-release tablet (15mg) or a single intravenous (iv) administration of methimazole (1 mL of a 9.2 g/L solution).

Table 2: Pharmacokinetics of thiamazole in cats ($n = 7$) following a single oral administration of carbimazole 15mg as a controlled-release tablet (Vidalta 15mg) or a single intravenous administration of thiamazole (1mL of 9.2g/L solution)

Parameter	Vidalta 15mg tablet	Thiamazole (intravenous injection)
Dose* (mg/kg)	3.4 ± 0.5	2.1 ± 0.3
C _{max} (µg/mL)	1.44 ± 0.35	-
t _{max} (h)	4 (4-8)	-
AUC (µg·h/mL)	1.3 ± 2.9	15.8 ± 4.9
t _{1/2} (h)	9.0 [†]	3.6
MRT (h)	8.9 (6.6-13.0)	6.2 (3.8-10.4)
Cl _{tot} (mL/h/kg)	134.2 ± 34.9	131.9 ± 38.9
V _z (mL/kg)	-	695.3 ± 169.0
Absolute bioavailability F (%)	88 ± 11	-

Values are arithmetic mean ± SD, except for t_{max} and MRT [median (range)] and t_{1/2} (harmonic mean).

*based on Vidalta 15mg being equivalent to 9.2mg thiamazole (molar ratio 1.63); [†]95% confidence

3.3 Effect of food intake on the pharmacokinetics of thiamazole after oral administration of Vidalta 15mg tablet¹⁰

Administration of Vidalta with food increases carbimazole absorption.

Method

The pharmacokinetics of thiamazole following oral administration of Vidalta 15mg tablets were compared in fasted and fed cats ($n=8$, 4 female, 4 male, aged 3.8 ± 1.3 years, weighing 3.8 ± 0.9 kg). A crossover (2 X 4) study design with a washout period of 4 days was used. All cats were fasted overnight and food was either supplied immediately after treatment (fed group) or 8 h after treatment (fasted group).

Results

The plasma concentrations of thiamazole vs. time profiles are shown in Figure 3. The pharmacokinetic parameters calculated are summarized in Table 3. C_{max} was significantly higher in the fed group compared to the fasted group ($P < 0.05$), whereas t_{max} was similar ($P > 0.05$). The AUC was about 1.4 times higher in the fed group than in the fasted group ($P = 0.066$).

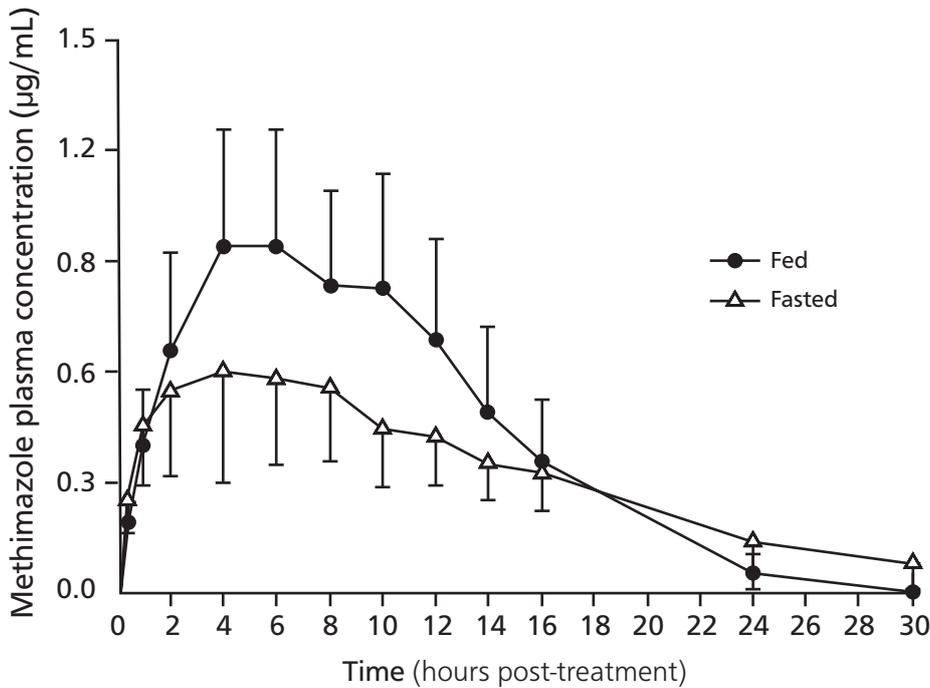


Fig 3. Plasma concentrations of methimazole (mean \pm SD) in fasted and fed cats ($n = 8$) following a single oral administration of a controlled-release carbimazole tablet (15mg).

Table 3: Pharmacokinetics of thiamazole in fasted and fed cats ($n = 8$) following a single oral administration of carbimazole 15mg as a controlled-release tablet (Vidalta 15mg)

Parameter	Fasted	Fed
C_{max} ($\mu\text{g/mL}$)	0.65 ± 0.29	$1.04 \pm 0.32^{\dagger,*}$
t_{max} (h)	5 (1-10)	6 (4-12)
AUC ($\mu\text{g h/mL}$)	9.65 ± 2.95	$12.39 \pm 3.32^{\dagger,**}$
Relative bioavailability F (%)	-	138 ± 53

Values are arithmetic mean \pm SD, except for t_{max} [median (range)].

† fasted vs. fed not bioequivalent [confidence limits outside the range (80-125) for the 90% confidence interval].

* $P < 0.05$; ** $P = 0.066$.

3.4 Pharmacokinetics of thiamazole after repeated oral administration of Vidalta 15mg tablets¹⁰

Repeated administration of Vidalta does not lead to thiamazole accumulation.

Method

Eight cats (4 female, 4 male, aged 2.6 ± 1.9 years, weighing $4.0 \pm 0.8\text{kg}$) had one Vidalta 15mg tablet administered once-daily for 13 consecutive days. Plasma concentrations of thiamazole were determined on the first and last days of treatment and before (trough) and 6 h after (peak) treatment every 2 or 3 days until the last day of treatment. The cats were fasted overnight and food was given immediately after treatment each day.

Results

The plasma concentrations of thiamazole vs. time profiles are shown in Figure 4. The pharmacokinetic parameters calculated are summarized in Table 4. The pharmacokinetic profiles after single and repeated administration of Vidalta 15mg were highly comparable. C_{trough} did not change significantly from day 2 to day 14 compared to the value on day 1, except on day 5 and day 9 ($P < 0.05$). C_{peak} on day 13 was only slightly increased from the basal value on day 1 ($P > 0.05$). Thiamazole concentrations reached basal concentrations within 24 h of the last treatment in all but one animal (32 h). A ratio of accumulation of 1.15 ± 0.37 (mean \pm SD) was calculated. No signs related to treatment were observed in the cats during the study.

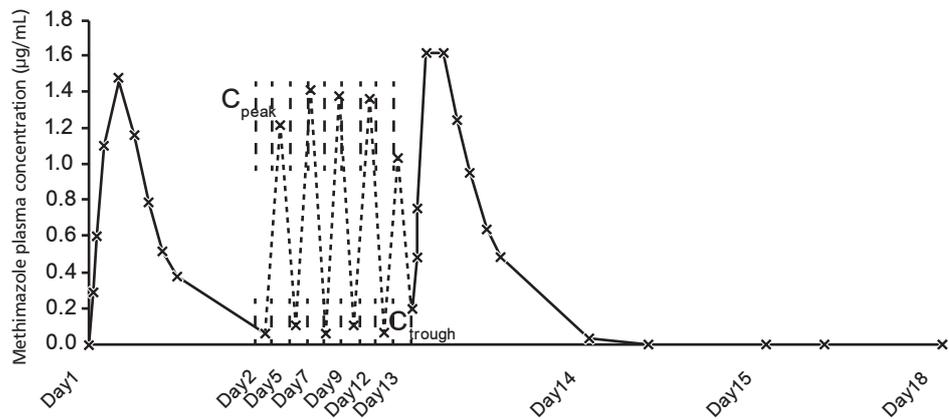


Fig 4. Plasma concentrations of methimazole (mean \pm SD) in cats ($n = 8$) following single and repeated oral administrations of a carbimazole controlled-release tablet (15mg).

Table 4: Pharmacokinetics of thiamazole following single and repeated oral administrations of a carbimazole 15mg controlled-release tablet (Vidalta 15mg) to cats ($n=8$).

Parameter	Single dose	Repeated dose
C_{max} ($\mu\text{g/mL}$)	1.51 ± 0.37	1.90 ± 0.68
t_{max} (h)	4 (4-6)	4 (2-8)
AUC ($\mu\text{g}\cdot\text{h/mL}$)	12.01 ± 3.44	13.45 ± 5.54
Rac*	-	1.15 ± 0.37

Values are arithmetic mean \pm SD, except for t_{max} [median (range)].

*accumulation ratio.

4 Clinical Studies

4.1 Clinical efficacy and safety of once-daily Vidalta 15mg in cats with hyperthyroidism¹¹

Vidalta provides rapid return of tT4 to within the reference interval and associated improvement of clinical signs, with the added benefit of once daily administration to increase owner compliance.

Method

A multicenter, self-controlled study in 44 client-owned cats with history and clinical signs of hyperthyroidism, and total thyroxine (tT4) concentration greater than or equal to 50 nmol/L.

Treatment was started at Vidalta 15mg once-daily, response assessed after 10 days, and 3, 5, 8, 26 and 53 weeks; dose adjusted as required. At each visit, food and water intake were recorded, a physical examination conducted and serum tT4, hematology and clinical biochemistry parameters were determined. The daily dose of Vidalta was adjusted based on both the clinical evaluation and tT4 concentration, using one or more of the available strengths (10 and 15mg tablets) given once-daily.

Dose adjustment had to be made by not more than a 5mg increment/decrement at each visit. Additional examinations could be conducted between the scheduled visits.

Evaluation of the efficacy of treatment was based on tT4 concentrations and on assessment of the clinical condition. Each cat was subjectively classified by the investigators as being hypothyroid, euthyroid or hyperthyroid based on changes in heart rate, bodyweight, appetite, water intake and behavior as compared with the previous visit. The investigators were blinded to the tT4 concentration at the time of classification.

Results

The 44 included cats (25 spayed female, 1 entire male and 18 neutered males) were 14 ± 3 years old (mean \pm SD) and weighed 3.5 ± 1.2 kg. The majority (42) were European short/long-hair. Three cats were treated for less than 10 days and were not examined again after inclusion.

A starting dose of Vidalta 15mg once-daily restored tT4 levels to within the reference range in 70% of cats within 10 days and 76% after three weeks.

The dose administered at the last visit ranged between 10 and 20mg in around 90% of the cats. Only one cat required a lower dose (10mg every other day) and one cat a higher dose (25mg once-daily).

A number of biochemical abnormalities were detected at inclusion, such as increased ALT and ALP, in more than half of the cats. The liver enzymes improved in around three-quarters of the cats during

treatment, and cats with liver enzymes in the reference range at presentation remained so throughout treatment.

Renal parameters were often within or close to the reference range at presentation, but tended to increase during treatment. Genuine renal decompensation was observed in one case only, but this cat was able to stay in the study and actually had tT4 within the reference range up to the final visit. No cases died or required treatment to be discontinued due to increase in BUN and creatinine. Concomitant hyperthyroidism and CKD are common in older cats.

Alterations in blood parameters (eosinophilia, lymphopenia, thrombocytopenia and leucocytosis) were also reported. These alterations were not present at inclusion and are more likely to be a direct effect of treatment.

The survival data showed that more than half of the population was still alive after one year of treatment which is in good agreement with a retrospective study with thiamazole where the survival time in half the population was about 18 months. Pre-existing illness (e.g. renal or hepatic disease) may impact survival time in cats undergoing medical treatment for hyperthyroidism.

Conclusion

This field trial demonstrates that Vidalta is effective in short and long-term treatment of cats with hyperthyroidism. Daily maintenance dose and safety profiles are in line with previous reports using carbimazole or thiamazole (not available in NZ) conventional tablets in the hyperthyroid cat population.

The reduced frequency of administration and the short period required to observe both tT4 normalization and clinical improvement after treatment initiation provides additional benefit to the cat and its owner, and is likely to improve overall compliance to treatment.

4.2 Long-term follow-up of hyperthyroid cats treated with Vidalta 10mg or Vidalta 15mg tablets¹²

Vidalta 10mg and Vidalta 15mg can be used long term to treat feline hyperthyroidism effectively and safely.

Method

Eighty-seven (87) out of 161 cats completed an initial six month field effectiveness study before continuing on long-term Vidalta therapy for up to four additional years. During this long-term safety study (March 2007 to April 2011), Vidalta was administered orally once-daily or every other day using a combination of Vidalta 10mg and Vidalta 15mg tablets. The dose was adjusted at the discretion of the attending veterinarian. Clinical signs and abnormal findings were monitored and recorded as adverse events.

Results

The median number of days on treatment for the entire study population over the entire treatment period was 603 days (range: 5 to 1612 days, $n=161$), with 18 cats still receiving treatment by 01 April 2011. Twenty-four cats were removed from the study for various reasons, including lack of owner compliance ($n=10$), or change of treatment ($n=9$). The remaining forty-five (45) cats either died ($n=10$) or were euthanized ($n=35$). Causes of death included neoplasia, gastrointestinal disease, dyspnea, or myocardial hypertrophy ($n=1$ each) or unknown ($n=6$). The most common reasons for euthanasia were worsening of the cat's clinical condition and poor quality of life ($n=10$), renal disease ($n=7$) or neoplasia ($n=4$).

Conclusions

Adverse events and clinical signs observed in this study are consistent with the use of mercaptoimidazoles (carbimazole and thiamazole [methimazole]) in cats and the occurrence of concomitant diseases commonly diagnosed in this age range. This study shows that administration of Vidalta once-daily or every other day allows the owners to be compliant with long-term therapy requirements. This study supports the long-term use of Vidalta 10mg and Vidalta 15mg tablets for the treatment of feline hyperthyroidism and its associated clinical signs.

5 Discussion & Conclusion

Hyperthyroidism is a frequently diagnosed endocrine disorder of cats. Both oral carbimazole and thiamazole have been widely used to treat feline hyperthyroidism for decades. Chronic medical therapy of feline hyperthyroidism can be managed with two to three times daily administration of carbimazole or thiamazole (using a total daily dose up to 25mg), although some cats showing moderate increase of total T4 concentration can be managed using a single daily treatment. However, once-daily dosing (5mg q 24 h) has been reported to be less effective than divided dosing (2.5mg q 12 h). Other current approaches include dietary management, with a restricted iodine diet, or a topical formulation of thiamazole that is applied topically to the pinnae.

The pharmacokinetic studies of Vidalta 15mg indicate that the novel tablet has controlled-release properties, as shown by a lack of pronounced peak and a sustained presence of thiamazole in plasma. The feeding status of the cat at the time of treatment influences the absorption of thiamazole from the gastrointestinal tract, the extent of absorption being improved by approximately 40% when Vidalta 15mg is administered with food. No accumulation of thiamazole is reported after repeated oral administration of Vidalta 15mg for 13 consecutive days. The pharmacokinetic profile of Vidalta 15mg supports its use as a once-daily treatment in hyperthyroid cats.

The clinical studies demonstrate that Vidalta 10mg and 15mg are effective in the short- and long-term treatment of cats with hyperthyroidism. Daily maintenance dose and safety profiles are in line with previous reports using carbimazole or thiamazole conventional tablets in the hyperthyroid cat population. The reduced frequency of administration and the short period required to observe both tT4 normalisation and clinical improvement after treatment initiation provides additional benefit to the cat and its owner, and is likely to improve overall compliance to treatment.

6 Product Summary

Vidalta 10mg are round pink tablets, each containing 10mg carbimazole and 0.25mg red ferric oxide (E172). Vidalta 15mg are round pink tablets, each containing 15mg carbimazole and 0.75mg red ferric oxide (E172).

6.1 Indications

For the treatment of hyperthyroidism and hyperthyroidism-associated clinical signs in cats.

6.2 Dosage and administration

For oral use only.

Vidalta tablets should be administered at the same time every day, in particular with relation to feeding. Do not break or crush Vidalta tablets as this will affect the sustained release properties of the tablet. The prolonged release formulation of Vidalta enables a 24 hour dosing interval. The aim of treatment is to maintain total thyroxin concentrations (tT4) in the lower end of the reference range. Accordingly, the following dose recommendations for dosing during adjustment and maintenance phases are suggested. However dosing adjustment should be primarily based upon the clinical assessment of the individual cat. Monitoring of tT4, full hematology and liver and kidney parameters is advised at each recommended follow-up visit.

6.2.1 Adjustment phase

The starting dose is a single daily oral administration of one tablet of Vidalta 15mg per cat. Consideration should be given to a starting dose of Vidalta 10mg daily where the tT4 concentration is only mildly increased, e.g. between 50 nmol/L and 100 nmol/L. With the recommended starting dose of one Vidalta 15mg tablet once-daily, tT4 may decrease to within euthyroid range (tT4 < 50 nmol/L) shortly after treatment initiation. A dose adjustment may be required as early as 10 days after commencing treatment. Dose adjustment should also be performed 3, 5 and 8 weeks after initiation of treatment, depending on both clinical and hormonal responses to treatment.

6.2.2 Maintenance phase

Follow-up visits every 3 to 6 months are recommended. The dose should be adjusted individually based on clinical signs and tT4. It is advisable to check tT4 10-14 days after dose adjustment. The therapeutic dose of Vidalta ranges between 10mg (one 10mg tablet) and 25mg (one 10mg and one 15mg tablet) once-daily. Some cats require doses less than 10mg carbimazole daily. Every other day dosing with Vidalta 10mg or Vidalta 15mg may be sufficient to control the disease. Dose increases should not be made in increments of greater than 5mg. Doses above 20mg have only been trialed in a small number of cats and should be used with caution.

6.3 Contraindications

Do not use in:

- cats with hematological disorders such as anaemia, neutropenia, lymphopenia and thrombocytopenia;
- cats with coagulopathies;
- pregnant or lactating queens;
- cats with hypersensitivity to mercaptomidazoles (carbimazole or thiamazole).

6.4 Precautions

Thiamazole (methimazole), the active metabolite of carbimazole, inhibits thyroid hormone production and therefore cessation of treatment with carbimazole will result in a rapid (within 48 hours) return to pre-treatment thyroid levels. Chronic administration is therefore necessary unless surgical or radiation-induced thyroidectomy is performed. A small proportion of cats with thyroid adenoma may fail to respond or have poor response to treatment. Thyroid carcinoma is a rare cause of hyperthyroidism in the cat and medical management alone is not recommended in such cases as it is not curative.

The safety of the veterinary medicinal product has not been established in pregnant or lactating queens. However, since thiamazole crosses the placenta, distributes into milk and reaches approximately the same concentration as in maternal serum, the product should not be used in pregnant and lactating queens. Concomitant treatment with phenobarbitone may reduce the clinical efficacy of carbimazole. The concomitant use of benzimidazole anthelmintics (fenbendazole and mebendazole) has been shown to reduce the hepatic oxidation of this therapeutic class and may therefore induce and increase their circulating rates. Accordingly, co-administration of carbimazole with a benzimidazole is not recommended.

Thiamazole may display immunomodulating properties. This should be taken into account when considering vaccination of the cat. In case of overdosage, adverse effects may include, but are not limited to: weight loss, inappetence, vomiting and lethargy. Coat and skin abnormalities (erythema, alopecia) as well as hematological/ biochemical changes (eosinophilia, lymphocytosis, neutropenia,

lymphopenia, slight leukopenia, agranulocytosis, thrombocytopenia or hemolytic anemia) may also appear. Hepatitis and nephritis have been reported. These adverse effects may become severe in cases of chronic overdosing. In most cases, adverse effects are reversible upon discontinuation of treatment and appropriate veterinary care. tT4 concentrations below the lower limit of the reference range may be observed during treatment, although this is rarely linked to overt clinical signs. Decreasing the dose will lead to an increase of the tT4. Dose adjustment should not be made based on tT4 only.

6.5 Adverse Reactions

The most common adverse reactions include: vomiting, diarrhoea, reduced appetite, loss of condition, lethargy, tachycardia, polyuria, polydipsia and dehydration.

Dermatological signs (pruritus, moist dermatitis, erythema, alopecia) have also been reported. These clinical signs are usually mild, adequately controlled by symptomatic therapy and do not require treatment discontinuation.

Weight loss, dyspnea, aggressiveness, disorientation, ataxia or pyrexia have also been reported in rare cases.

Treatment of hyperthyroidism may result in a reduction of glomerular filtration rate (GFR). This can lead to the unmasking of pre-existing renal dysfunction. Renal function should therefore be monitored (BUN and creatinine) before and during treatment, preferably at each visit of the dose adjustment and maintenance phases. The dose should be adjusted according to the risk assessment of the individual case.

Treatment of hyperthyroidism with carbimazole may also induce elevation of liver enzymes (ALKP and ALT) or a worsening of pre-existing hepatic disorders. Liver enzymes should therefore be monitored before and during treatment, preferably at each visit of the dose adjustment and maintenance phases. Liver enzyme elevations are usually reversible following drug discontinuation, although symptomatic therapy (nutritional and fluid support) may be required. Severe cases may require temporary or permanent treatment discontinuation.

Anemia, increase or decrease in white blood cell count, neutrophilia, thrombocytopenia, eosinophilia and/or lymphopenia may also occur, in particular during the first 4-6 weeks of treatment. Hematology parameters should therefore be monitored on a regular basis before and during treatment, preferably at each visit of the dose adjustment and maintenance phases. Treatment discontinuation may be required in cases of persistent and marked disorder. In most of the cases, the abnormality will resolve spontaneously within one month after treatment discontinuation. Positive antinuclear antibody titers have also been reported.

Doses above 20mg have only been trialled in a small number of cats. Adverse reactions may occur at this dose, therefore careful monitoring is recommended and the dose should be adjusted according to the risk assessment of the individual case.

6.6 Safety Directions

Vidalta should be used for oral treatment of cats only. Wash hands with soap and water after handling the tablet or litter used by treated cats. Do not eat, drink or smoke while handling the tablet or used litter. Do not handle this product if you are allergic to hyperthyroidism inhibitors. As carbimazole is a suspected human teratogen, women of child-bearing age should wear gloves when handling litter and/or vomitus of treated cats. In the case of accidental ingestion, seek medical advice immediately and show the package insert or the label to the doctor.

See Safety Data Sheet for further information:
www.msd-animal-health.co.nz

6.7 First Aid

If swallowed do not induce vomiting. If poisoning occurs, contact a doctor or NZ Poisons Centre. Phone 0800 POISON (0800 764 766).

6.8 Disposal

Dispose of used package in household rubbish or recycle. Unused tablets should be returned to a veterinary clinic.

6.9 Storage

Store below 25°C. Protect from humidity and light. Keep the plastic container tightly closed to protect from moisture. Do not remove desiccant.

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