PRESCRIPTION ANIMAL REMEDY
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS
FOR ANIMAL TREATMENT ONLY

Palladia®

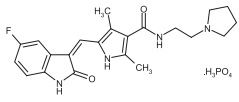
10 mg 15 mg 50 mg

Toceranib phosphate tablets

INDICATIONS
PALLADIA tablets are indicated for the treatment of Patnaik grade II or III, recurrent, cutaneous mast cell tumours with or without regional lymph node involvement in dogs.

Anti-neoplastic for oral use in dogs only

DESCRIPTION
PALLADIA, a multi-kinase inhibitor targeting several receptor tyrosine kinases (RTK), is the phosphate salt of toceranib. The empirical formula is $C_{22}H_{25}FN_4O_2H_3O_4P$ and the molecular weight is 494.46. The chemical name is (Z)-5-[(5-Fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]-2,4-dimethyl-N-(2-pyrrolidin-1-ylethyl)-1Hpyrrole-3-carboxamide phosphate. Toceranib phosphate is a small molecule with an indolinone chemical structure. The chemical structure of toceranib phosphate is:



CLINICAL PHARMACOLOGY
Mechanism of Action
Toceranib phosphate is a small molecule, multi-kinase inhibitor, that has demonstrated direct anti-tumour and antiangiogenic activity in *in vivo* and *in vitro* studies. Data from unpublished, biochemical and cellular studies suggest that toceranib selectively inhibits the tyrosine kinase activity of several members of the split kinase receptor tyrosine kinase (RTK) family, some of which are implicated in tumour growth, pathological angiogenesis, and metastatic progression of cancer. These include Flk-1/KDR tyrosine kinase (vascular endothelial growth factor receptor, VEGFR2), platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (kit). Toceranib treatment can induce cell cycle arrest and subsequent apoptosis in tumour cell lines expressing activating mutations in the split kinase RTK, *c-kit*. Canine mast cell tumour growth is frequently driven by activating mutations in *c-kit*.[1,2]

Pharmacokinetics
Following intravenous administration, the pharmacokinetics of toceranib is characterised by a very large volume of distribution (>20 L/kg, indicating partitioning into tissues), a terminal elimination half-life of about 16 hrs, and a clearance of >1 L/hr/kg. With a regimen of 3.25 mg free base equivalent (fbe)/kg doses of toceranib administered by tablet orally every second day for 2 weeks (7 doses), the pharmacokinetic parameters of toceranib in plasma in healthy Beagle dogs (between 7.2 – 12.5 kg) are shown in the table below.

Table 1: Pharmacokinetic Parameters

Pharmacokinetic Parameters (Mean + 1 SD)	Total (n=11; 6M, 5F) Dose 1	Total (n=10; 5M, 5F) Dose 7
Elimination half-life, $T_{1/2}$ (hr)	16.4±3.6	17.2±3.9
Time to maximum plasma concentration T_{max} (hr)	5.3±1.6	6.2±2.6
Maximum plasma concentration C_{max} (ng/mL)	86±22	109±41
C_{min} (ng/mL) [a, b]	12.7±6.0	18.7±8.3
Area under the plasma concentration time-curve, $AUC_{0\text{-}48}$ (ng·h/mL) [a]	1833±508	2635±939

a Dose-normalised value (adjusted to 3.25 mg/kg dose)
b C_{min} is the concentration at 48 h post-dose, which corresponds to the dose interval.

Oral bioavailability of toceranib is 77%. PALLADIA is highly protein bound at 91% to 93%. It should be noted that despite the homogeneity of subjects included in this study, large between-subject variability was observed. Regardless of the route of administration, linear pharmacokinetics has been observed at doses up to 5 mg/kg twice daily. Using an *in vitro* hepatocyte and liver microsome test system, the Z isomer was found to be metabolised to the N-oxide derivative of toceranib in dogs, humans, cats, and rats. Although a small gender difference was observed in the *in vitro* study (81% conversion in male dogs, 56% conversion in female dogs) no differences in toceranib pharmacokinetics was observed *in vivo*. The effects of renal impairment, hepatic impairment or breed on the pharmacokinetics of toceranib have not been investigated.

EFFECTIVENESS
The effectiveness and safety of PALLADIA oral tablets for the treatment of mast cell tumours was evaluated in a randomised, placebo-controlled, double-blinded, multicentred clinical field study. The purpose of this study was to evaluate the effectiveness and safety of PALLADIA in the treatment of mast cell tumours in dogs that had recurrent measurable disease after surgery and to evaluate objective response (complete or partial response). PALLADIA treatment was compared to placebo treatment using response rates at the end of the 6-week blinded phase. Response rates were determined using the US National Cancer Institute's Response Evaluation Criteria in Solid Tumours Guideline 3 which was modified specifically for the evaluation of canine mast cell tumours. One-hundred-fifty-three dogs were randomly assigned to treatment with either 3.25 mg/kg PALLADIA (n = 88) or placebo (n = 65) orally, every other day for 6 weeks, or until disease progression or withdrawal from the study for another cause.

The effectiveness analysis showed a statistically significant advantage for PALLADIA over placebo in the primary effectiveness endpoint of objective response at the end of the blinded phase. The results in Table 2 are for the blinded phase of the study. Objective response is defined as the sum of the complete and partial responses. Partial response is ≥30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum, non-progression of non-target lesions and appearance of no new lesions.

Table 2: Mast Cell Tumour – Primary Effectiveness Endpoint Results

Effectiveness Parameter	Placebo (n=63)	PALLADIA (n=86)	P-value
Objective Response Rate*	7.9%	37.2%	<0.001

* The difference in objective response rate between groups was not significantly associated with tumour burden (presence vs. absence of regional lymph node involvement) or tumour grade (P > 0.05).

Treatment was unblinded at the time of disease progression. Dogs receiving placebo were offered crossover to open-label PALLADIA; dogs receiving PALLADIA who displayed progressive disease in the blinded phase were discontinued from the study. Out of the 151 dogs entered in the blinded phase, 111 continued onto the next, extended phase of the study. For the placebo-escape dogs, the reference baseline for response calculations used the tumour assessments obtained just prior to the first dose of PALLADIA. The primary effectiveness endpoint of the extended phase was the biological response rate. The biological response rate is defined as the sum of the complete and partial responses, and the stable disease response. Complete and partial response definitions are consistent with the blinded phase, and stable disease is defined as no new lesions and absence of criteria for response or progressive disease. The biological response rate for the extended phase of the study was 59.5%.

Dogs were required to have Patnaik grade II or III, recurrent, cutaneous mast cell tumours with or without regional lymph node involvement. At least 1 tumour had to be at least 20 mm in diameter. Dogs had a limit of 1 completed radiation protocol and a limit of 1 prior systemic chemotherapy regimen. Dogs with evidence of systemic mast cell tumour were excluded. Treatment with systemic corticosteroids during the study or within 14 days prior to study initiation was not permitted. If needed to manage adverse reactions, dose interruptions (cessation of PALLADIA for up to 2 weeks) were prescribed and/or dosage was reduced to as low as 2.2 mg/kg.

Tumours of enrolled dogs were evaluated for the presence of a *c-kit* internal tandem duplication (ITD). During the combined blinded and open label phases, dogs whose tumours were positive for the *c-kit* ITD had a higher objective response rate compared to those negative for the *c-kit* ITD.

During the study, PALLADIA was administered concomitantly with other medications such as antimicrobials, H-2 receptor blockers, antihistamines, anti-emetics, non-steroidal anti-inflammatory drugs, locally-acting anti-ulcer medications, opiate gastro-intestinal motility modifiers, opioids, vaccines, anthelmintics, antiparasitics, and topical/ophthalmic/otic corticosteroid preparations. During the open-label phase only, 5 dogs received a brief course of short-acting corticosteroids.
The duration of treatment with PALLADIA ranged from 2 to 812 days (mean, 144 days; median, 68 days). All dogs received at least 1 dose of PALLADIA.

ANIMAL SAFETY
In the target animal safety study presented below, PALLADIA was demonstrated to have a narrow margin of safety. Dogs being treated with PALLADIA should be monitored for adverse reactions which may indicate a dose adjustment is required. Toceranib was administered orally to 20 male and 20 female adult Beagle dogs (approximately 2 years of age) at doses of 0 mg/kg (placebo, 12 dogs), 2 mg/kg (0.5X, 8 dogs), 4 mg/kg (1X, 12 dogs), or 6 mg/kg (1.5X, 8 dogs) once every other day for 13 consecutive weeks without dose interruption. Toceranib caused weight loss, decreased feed consumption, pancreatic, gonadal, adrenal, muscle, and haematopoietic changes. Feed consumption was decreased in the 6 mg/kg group compared to placebo, with the largest difference in means occurring at Day 35. Decrease in body weights in the 4 mg/kg group were seen at Day 31 and in the 6 mg/kg group at Day 15 compared with placebo and continued through the study. Dose related lameness, observed almost exclusively in the hind limbs, and limb pain was greater in all treatment groups as compared to placebo, with the 6 mg/kg group demonstrating the highest incidence. Stiffness and weakness were noted to occur almost exclusively in the 6 mg/kg group. Redness of oral mucosa was observed in all treatment groups. One dog in the 4 mg/kg group had oral ulcerations and one dog in the 6 mg/kg group had skin ulcerations, both with bacterial infections present. Diarrhoea or soft stools were seen in all four groups.

Haematology analyses showed decreases in haematocrit, haemoglobin, and erythrocyte count and a decrease in reticulocyte count in the 4 and 6 mg/kg groups that tended to recover sufficiently to limit further erythrocyte count decreases. White blood cell counts were significantly lower across the study in all treated groups compared to placebo, primarily due to a decrease in neutrophils. Lymphocytes decreased to a lesser degree, especially at the low dose. Eosinophils and basophils showed marked, persistent decreases. Monocytes were not affected. Platelet counts increased slightly in 4 and 6 mg/kg groups. Increases were observed in fibrinogen in the 4 and 6 mg/kg group. Increases were observed in aspartate aminotransferase, creatine kinase, and serum phosphorus concentrations in the 4 and 6 mg/kg groups. Increases in alkaline phosphatase were seen in the 6 mg/kg group. An increase in amylase was seen in one dog in each of the treatment groups. An increase in serum potassium was seen in one dog in the 6 mg/kg group. Increases in lactate dehydrogenase and globulins were observed in the 6 mg/kg group. Treatment-related microscopic changes included slight to marked reduction in cellularity of sternal and femoral bone marrow. There was a corresponding mild extramedullary haematopoiesis, mainly erythropoiesis, in the spleen. In the pancreas, dose-related slight to moderate acinar degranulation, characterised by diffuse loss of zymogen granules, occurred. In the adrenal glands, minimal cortical congestion/haemorrhage occurred at all doses, with suggestive dose-relationship. Adrenal cortical vacuolation was noted with low frequency in all groups. Dose related changes were noted in reproductive organs of both sexes. Males showed a dose-related germ cell depletion, tubular vacuolation, and reductions in numbers of mature spermatozoa. In females, ovaries showed a reduced incidence of mature/regressing corpora lutea and an increased incidence of small follicles. Two dogs (one male, one female) in the 6 mg/kg group were euthanised for treatment-related clinical toxicities on Days 23 and 27 of the study, respectively. Onset of the terminal syndrome was seen as markedly reduced feed intake and melaena. Over the following 9 days, the decreased feed intake progressed to near-complete anorexia and haematochezia appeared. Weight loss, lethargy, hindlimb lameness and weakness were observed. The following clinical pathology results are consistent with changes seen in the other dogs in the 6 mg/kg group as well as changes due to the dogs' debilitated conditions just prior to euthanasia. Both dogs had increases in total protein, globulins, phosphorus, cholesterol, triglycerides and fibrinogen. One dog had pancytopenia, decreased haematocrit, haemoglobin, reticulocytes, albumin, and PT and increased bands. Haematuria was also present. The other dog also had decreased lymphocytes, eosinophils, chloride, and sodium and increases in RBC, haematocrit, haemoglobin, platelets, ALP, amylase, creatinine, BUN, magnesium, potassium, and total bilirubin. Clotting profile showed a decreased PT and increased PTT in both dogs. These dogs showed lymphoid depletion in lymph nodes, thymus, and gut-associated lymphatic tissues and mild to marked gastrointestinal lesions in addition to the microscopic findings described in animals surviving to the end of the study. These two dogs also had lesions in the gastrointestinal tract, kidneys, pancreas, pituitary gland and adrenal glands.

DIRECTIONS FOR USE
Contraindications:
This product is contraindicated for use in breeding dogs and pregnant or lactating bitches.

Other compounds in the antiangiogenesis class of antineoplastic agents are known to increase embryolethality and foetal abnormalities. As angiogenesis is a critical component of embryonic and foetal development, inhibition of angiogenesis following administration of PALLADIA should be expected to result in adverse effects on the pregnancy in the bitch.

Precautions
The safe use of PALLADIA has not been evaluated in dogs less than 24 months of age or weighing less than 5 kg, therefore more intensive monitoring of dogs in these classes should be undertaken.

To appropriately use the dose modification table, it is advised that a complete blood cell count, serum chemistry panel and urinalysis be conducted prior to initiation of treatment and approximately one month after treatment is initiated; thereafter at approximately six week intervals or as determined by the veterinarian. Periodic monitoring of laboratory variables should be completed in the context of the clinical signs and condition of the animal and results of laboratory variables at prior visits.

PALLADIA may cause vascular dysfunction which can lead to oedema and thromboembolism, including pulmonary thromboembolism. Discontinue drug until clinical signs and clinical pathology have normalised. To assure vasculature homeostasis, wait at least 3 days after stopping drug before performing surgery.
Serious and sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred rarely in dogs treated with PALLADIA. If gastrointestinal ulceration is suspected, stop drug administration and treat appropriately.

Temporarily discontinue the use of PALLADIA if anaemia, azotaemia, hypoalbuminaemia, and hyperphosphataemia occur simultaneously. Resume treatment at a dose reduction of 0.5 mg/kg after 1 to 2 weeks when values have improved and albumin is >2.5 g/dL. Temporary treatment interruptions may be needed if any one of these occurs alone: haematocrit <26%, creatinine ≥2.0 mg/dL or albumin <1.5 g/dL. Then resume treatment at a dose reduction of 0.5 mg/kg once the haematocrit is >30%, the creatinine is <2.0 mg/dL, and the albumin is >2.5 g/dL.

Temporarily discontinue the use of PALLADIA if neutrophil count is ≤1000/µL. Resume treatment after 1 to 2 weeks at a dose reduction of 0.5 mg/kg, when neutrophil count has returned to >1000/µL. Further dose reductions may be needed if severe neutropenia reoccurs. The presence of systemic mast cell tumour prior to treatment may predispose a dog to clinically significant mast cell degranulation with possible severe systemic adverse reactions when treated with PALLADIA. Attempts should be made to rule out systemic mastocytosis prior to initiation of treatment with PALLADIA.

PALLADIA has been associated with severe diarrhoea or GI bleeding that requires prompt treatment. Dose interruptions and dose reductions may be needed depending upon the severity of clinical signs. Use non-steroidal anti-inflammatory drugs with caution in conjunction with PALLADIA due to an increased risk of gastrointestinal ulceration or perforation. PALLADIA is metabolised in the liver and should be used with caution in dogs suffering from hepatic disease.
Treatment should be permanently discontinued if severe adverse events recur or persist despite appropriate supportive care and dose reduction as described in Table 6.

Co-administration of PALLADIA with strong inhibitors of the CYP3A4 family may increase PALLADIA concentrations. The effect of concomitant medications that may inhibit the metabolism of PALLADIA has not been evaluated. Specific interactions with other medications administered concomitantly have not been studied. Drug compatibility should be monitored in patients requiring concomitant medications.

ADVERSE REACTIONS
A US clinical field study comprised of a 6-week blinded phase, followed by an open-label phase, evaluated the safety and effectiveness of PALLADIA in 151 client-owned dogs that had Patnaik grade II or III, recurrent, cutaneous mast cell tumours with or without regional lymph node involvement. The most common adverse reactions reported during the blinded phase are summarised in Table 3; those reported during the entire study (blinded phase combined with the open-label phase) are summarised in Table 4.

Table 3. Summary of the most common adverse reactions during the blinded phase[a]

Adverse Reaction	Placebo (n = 64)		PALLADIA (n = 87)	
	Any Grade[b]	Grade 3 or 4[b]	Any Grade[b]	Grade 3 or 4[b]
Diarrhoea	26.6%	3.1%	46.0%	6.9%
Anorexia	31.3%	6.3%	39.1%	6.9%
Lethargy	29.7%	3.1%	35.6%	4.6%
Vomiting	32.8%	6.3%	32.2%	9.2%
Lameness	9.4%	0.0%	17.2%	0.0%
Weight Loss	3.1%	0.0%	14.9%	1.1%

PRESCRIPTION ANIMAL REMEDY
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS
FOR ANIMAL TREATMENT ONLY

Palladia®

10 mg 15 mg 50 mg

Toceranib phosphate tablets

Adverse Reaction	Placebo (n = 64)		PALLADIA (n = 87)	
	Any Grade[b]	Grade 3 or 4[b]	Any Grade[b]	Grade 3 or 4[b]
Blood in stool/ GI bleed/ haemorrhagic diarrhoea	3.1%	0.0%	12.6%	2.3%
Musculoskeletal disorder	6.3%	0.0%	11.5%	1.1%
Dehydration	4.7%	0.0%	9.2%	2.3%
Dermatitis	9.4%	1.6%	9.2%	0.0%
Pruritis	4.7%	0.0%	9.2%	0.0%
Tachypnoea	4.7%	0.0%	8.0%	1.1%
Localised pain	4.7%	0.0%	8.0%	0.0%
Nausea	3.1%	0.0%	8.0%	1.1%
General pain	4.7%	1.6%	6.9%	0.0%
Polydipsia	7.8%	0.0%	6.9%	0.0%
Pyrexia	3.1%	0.0%	5.7%	2.3%
Flatulence	3.1%	0.0%	5.7%	0.0%
Pigmentation disorder	1.6%	0.0%	5.7%	0.0%
Laboratory Abnormality	**Any Grade[c]**	**Grade 3 or 4[c]**	**Any Grade[c]**	**Grade 3 or 4[c]**
Neutropenia	6.3%	0.0%	46.0%	0.0%
Thrombocytopenia	20.3%	0.0%	24.1%	0.0%
Increased alanine aminotransferase	21.9%	4.7%	24.1%	1.1%
Hypoalbuminaemia	7.8%	0.0%	12.6%	0.0%
Decreased haematocrit	7.8%	0.0%	5.7%	3.4%
Hyperbilirubinaemia	1.6%	1.6%	5.7%	0.0%
Increased creatinine	4.7%	0.0%	5.7%	0.0%
Urinary tract infection	1.6%	0.0%	5.7%	0.0%

[a] The mean time on study during the blinded phase was 37.0 days for PALLADIA-treated dogs (median, 42.0 days) and 27.6 days for placebo-treated dogs (median, 21.0 days); no adjustments were made in the statistical comparisons for this disparity.
[b] Investigators assigned severity grade of 1, 2, 3 or 4 (1 - least severe; 4 - most severe).
[c] Grading of laboratory abnormalities was based on the US National Cancer Institute's Common Toxicity Criteria guideline adapted for canines (1 - least severe; 4 - most severe).

Table 4. Summary of the most common adverse reactions during the study (blinded phase combined with the open-label phase)[a]

Adverse Reaction	PALLADIA (n = 145)	
	Any Grade[b]	Grade 3 or 4[b]
Diarrhoea	58.6%	8.3%
Anorexia	49.7%	8.3%
Vomiting	47.6%	9.7%
Lethargy	39.3%	4.1%
Lameness	22.8%	0.0%
Weight Loss	21.4%	2.8%
Blood in stool/GI bleed/ haemorrhagic diarrhoea	18.6%	2.8%
Dehydration	15.2%	2.1%
Pruritis	12.4%	0.0%
Pigmentation disorder	11.7%	0.0%
Dermatitis	11.0%	0.0%
Musculoskeletal disorder	11.0%	0.0%
General pain	8.3%	0.0%
Otitis externa	8.3%	0.0%
Tachypnoea	8.3%	0.0%
Nausea	7.6%	1.4%
Polydipsia	7.6%	0.0%
Pyrexia	6.9%	2.8%
Arthritis	6.2%	0.0%
Localised oedema	6.2%	0.0%
Bacterial skin infection	5.5%	0.0%
Conjunctivitis	5.5%	0.0%
Laboratory Abnormality	**Any Grade[c]**	**Grade 3 or 4[c]**
Neutropenia	44.8%	1.4%
Hypoalbuminaemia	28.3%	1.4%
Thrombocytopenia	28.3%	2.1%
Increased alanine aminotransferase	27.6%	4.1%
Decreased haematocrit	11.0%	2.8%
Increased creatinine	13.8%	1.4%
Hyperbilirubinaemia	6.9%	0.0%
Urinary tract infection	7.6%	0.0%

[a] The duration of treatment with PALLADIA ranged from 2 to 812 days (mean, 144 days; median, 68 days). All dogs received at least 1 dose of PALLADIA.
[b] Investigators assigned severity grade of 1, 2, 3 or 4 (1 – least severe; 4 – most severe).
[c] Grading of laboratory abnormalities was based on the US National Cancer Institute's Common Toxicity Criteria guideline adapted for canines (1 – least severe; 4 – most severe).
Other adverse events were reported but occurred in < 5% of dogs.
Any individual dog may have had multiple adverse events.

There were 5 deaths during this study that were possibly drug related. Pathology findings generally revealed evidence of vascular dysfunction including pulmonary thromboembolism (post-operative); multi-organ failure associated with vasculitis and thrombosis; vascular thrombosis with disseminated intravascular coagulopathy (DIC) and pancreatitis; and vasculitis with DIC. One dog died secondary to gastric perforation; the duration of treatment with PALLADIA was 221 days and there was no evidence of mast cell tumour at necropsy. These deaths occurred in the presence or absence of gross disease; treatment durations ranged from 18 to 221 days.

The relationship of the following deaths to drug are unknown. One dog, first treated for 3 weeks with a placebo, died of unknown cause 7 days after initiation of PALLADIA therapy. Another dog died of unknown cause 92 days after initiation of PALLADIA therapy. No necropsy was conducted in either dog. Twenty seven dogs developed some form of gastrointestinal bleeding with 2.8% of dogs having severe bleeding. One dog developed gastric ulceration which was possibly drug related. Three dogs died from gastric (1 dog) or duodenal (2 dogs) perforations during the study. One dog with a duodenal perforation received only 1 dose of study drug and, therefore, was not considered drug related. Seven dogs developed nasal depigmentation within the first few weeks of treatment. Eleven dogs developed coat colour or skin changes during the study. Two of these dogs had complete coat colour changes from fawn to white and from deep red to blonde. Seven dogs experienced alopecia. There is a drug related effect on body weight: 20.0% of dogs had >13% weight loss in the blinded plus open-label phase attributable to drug. Of these, 5 dogs had >25% weight loss. Three dogs had seizure-like activity while on study drug. It can not be determined if these were drug related. Two dogs developed epistaxis that was not associated with thrombocytopenia. Another dog developed epistaxis with concurrent disseminated intravascular coagulopathy.

DOSAGE AND ADMINISTRATION
TABLETS MUST NOT BE SPLIT. DO NOT BREAK OR CRUSH TABLETS.

Administer an initial dosage of 3.25 mg/kg body weight, orally every second day (see **Table 5**). Dose reductions of 0.5 mg/kg (to a minimum dose of 2.2 mg/kg every second day) and dose interruptions (cessation of PALLADIA for up to two weeks) may be utilised, if needed, to manage adverse reactions. Adjust dose based on approximately weekly veterinary assessments for the first 6 weeks and approximately every 6 weeks, thereafter. PALLADIA may be administered with or without food.

Stop PALLADIA immediately and contact your veterinarian if you notice any of the following changes in your dog:
- Refusal to eat
- Vomiting or watery stools (diarrhoea), especially if more frequent than twice in 24 hours
- Black tarry stools
- Bright red blood in vomitus or stools
- Unexplained bruising or bleeding
- Or if your dog experiences other changes that concern you

There are other side effects which may occur. For a more complete list, ask your veterinarian.

Table 5. 3.25 mg/kg Dose Chart

Dog Bodyweight (kg)	Number of Tablets				
	10 mg (blue)		15 mg (orange)		50 mg (red)
5.0* – 5.3			1		
5.4 – 6.9	2				
7.0 – 8.4	1	plus	1		
8.5 – 10.0			2		
10.1 – 11.5	2	plus	1		
11.6 – 13.0	1	plus	2		
13.1 – 14.6			3		
14.7 – 16.1					1
16.2 – 17.6	1	plus	3		
17.7 – 19.2	1			plus	1
19.3 – 20.7			1	plus	1
20.8 – 23.0	2			plus	1
23.1 – 26.9			2	plus	1
27.0 – 29.9			3	plus	1
30.0 – 32.3					2
32.4 – 34.6	1			plus	2
34.7 – 36.1			1	plus	2
36.2 – 38.4	2			plus	2
38.5 – 43.0			2	plus	2
43.1 – 47.6					3
47.7 – 49.9	1			plus	3
50.0 – 51.5			1	plus	3
51.6 – 53.8	2			plus	3
53.9 – 58.4			2	plus	3
58.5 – 63.0*					4

* the number of tablets required for dogs below 5.0 kg or above 63 kg bodyweight, should be calculated based on the 3.25 mg/kg dosage regimen.

Table 6. Dose Modification Based on Toxicity Observed

Toxicity	Dose Adjustment
Anorexia	
<50% food intake ≥2 days	Discontinue treatment and institute dietary modification ± supportive care until food intake improves, then decrease dose by 0.5 mg/kg
Diarrhoea	
<4 watery stools/ day for less than 2 days	Maintain dose level and institute supportive care
≥4 watery stools/ day or ≥2 days	Discontinue treatment until formed stools and institute supportive care. When dosing is resumed, decrease dose by 0.5 mg/kg
Gastrointestinal Bleeding	
Fresh blood in stool or black tarry stool for >2 days or frank haemorrhage or blood clots in stool	Discontinue treatment and institute supportive care until resolution of all clinical signs of blood in stool, then decrease dose by 0.5 mg/kg
Hypoalbuminaemia	
<1.5 g/dL	Discontinue treatment until >2.5 g/dL, then decrease dose by 0.5 mg/kg
Neutropenia (neutrophil count)	
>1000/µL	Maintain dose level
≤1000/µL or neutropenic fever or infection	Discontinue treatment until >1000/µL and clinical signs normal, then decrease dose by 0.5 mg/kg
Anaemia (haematocrit)	
<26%	Discontinue treatment until >30%, then decrease dose by 0.5 mg/kg
Hepatic Toxicity (ALT, AST)	
>1X - 3X upper normal limit	Maintain dose level; stop hepatotoxic drugs, if used
>3X upper normal limit	Stop treatment until ≤3X upper normal limit, stop hepatotoxic drugs if used, then decrease dose by 0.5 mg/kg
Renal Toxicity (creatinine)	
<2.0 mg/dL	Maintain dose level
≥2.0 mg/dL	Discontinue treatment until <2.0 mg/dL, then decrease dose by 0.5 mg/kg
Concurrent anaemia, azotaemia, hypoalbuminaemia and hyperphosphataemia	
Discontinue treatment for 1 to 2 weeks until values have improved and albumin >2.5 g/dl, then decrease dose by 0.5 mg/kg.	

SAFETY DIRECTIONS
Wash hands after use.

GENERAL SAFETY PRECAUTIONS
DO NOT BREAK OR CRUSH TABLETS.
Toceranib may cause birth defects. For pregnant women, accidental ingestion of PALLADIA may have adverse effects on pregnancy.
Women of child bearing age are advised to wear gloves when administering this product and should pay special attention to these handling precautions.
Pregnant women and nursing mothers should not routinely administer PALLADIA, should avoid contact with faeces, urine and vomitus from treated dogs and broken or moistened PALLADIA tablets.
Children should not come into contact with this drug. Keep children away from vomitus, faeces and urine of treated dogs.
To avoid exposure to drug, wash hands with soap and water after administering PALLADIA and wear protective gloves to prevent direct contact with vomitus, faeces and urine of treated dogs and/or when cleaning up broken or moistened tablets.

ADDITIONAL SAFETY INFORMATION
PALLADIA, like other drugs in its class, prevents the formation of new blood vessels in tumours. In a similar manner, PALLADIA may affect blood vessel formation in the developing foetus and may harm an unborn baby.

Place all waste materials in a plastic bag and seal before general disposal. If eyes are accidentally exposed to the drug, rinse eyes with water immediately. In case of accidental ingestion by a person, seek medical advice immediately, show the package leaflet or label to the physician. Gastrointestinal discomfort such as vomiting or diarrhoea may occur if this drug is accidentally ingested.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131126. New Zealand 0800 764 766.
Refer to the material safety data sheet.

STORAGE
Store below 30°C (Room Temperature).

PRESENTATION
PALLADIA tablets contain 10 mg, 15 mg, or 50 mg of toceranib as toceranib phosphate per tablet. Each tablet is marked with the tablet strength on one side and the Zoetis logo on the other.

DISPOSAL
Dispose of empty container by wrapping with paper and putting in garbage.

WARRANTY
The manufacturer of this animal remedy extends/ grants to the purchaser a warranty that this animal remedy is reasonably fit for the purposes for which its use is recommended, provided that the purchaser uses the remedy only for the purposes for which it is recommended and strictly in accordance with the directions on this container.

TECHNICAL INFORMATION
Australia: 1800 814 883 TOLL FREE from anywhere in Australia
New Zealand: 0800 650 277 TOLL FREE from anywhere in New Zealand

APVMA Approval Numbers: 64617/57346 (10mg), 64616/57345 (15mg), 64615/57344 (50mg)

NEW ZEALAND INFORMATION
Restricted Veterinary Medicine
Registered pursuant to the ACVM Act 1997, No. A10834
See www.foodsafety.govt.nz for conditions of registration
Approved pursuant to the HSNO Act 1997, No. HSR100757
See www.epa.govt.nz for approval controls

Made in Italy

Zoetis Australia Pty Ltd
38-42 Wharf Road
West Ryde NSW 2114, Australia
www.zoetis.com.au

Zoetis New Zealand Limited
14 Normanby Road, Mt Eden, Auckland, New Zealand
www.zoetis.co.nz

References
1. London CA, Hannah AL, Zadovoskaya R, et al. Phase I Dose-Escalating Study of SU11654, a Small Molecule Receptor Tyrosine Kinase Inhibitor, in Dogs with Spontaneous Malignancies. Clinical Cancer Research 9(7):2755-2768; 2003.
2. Pryer NK, Lee LB, Zadovoskaya R, et al. Proof of Target for SU11654: Inhibition of KIT phosphorylation in Canine Mast Cell Tumors. Clinical Cancer Research 9(15):5729-5734; 2003.

May, 2013

zoetis