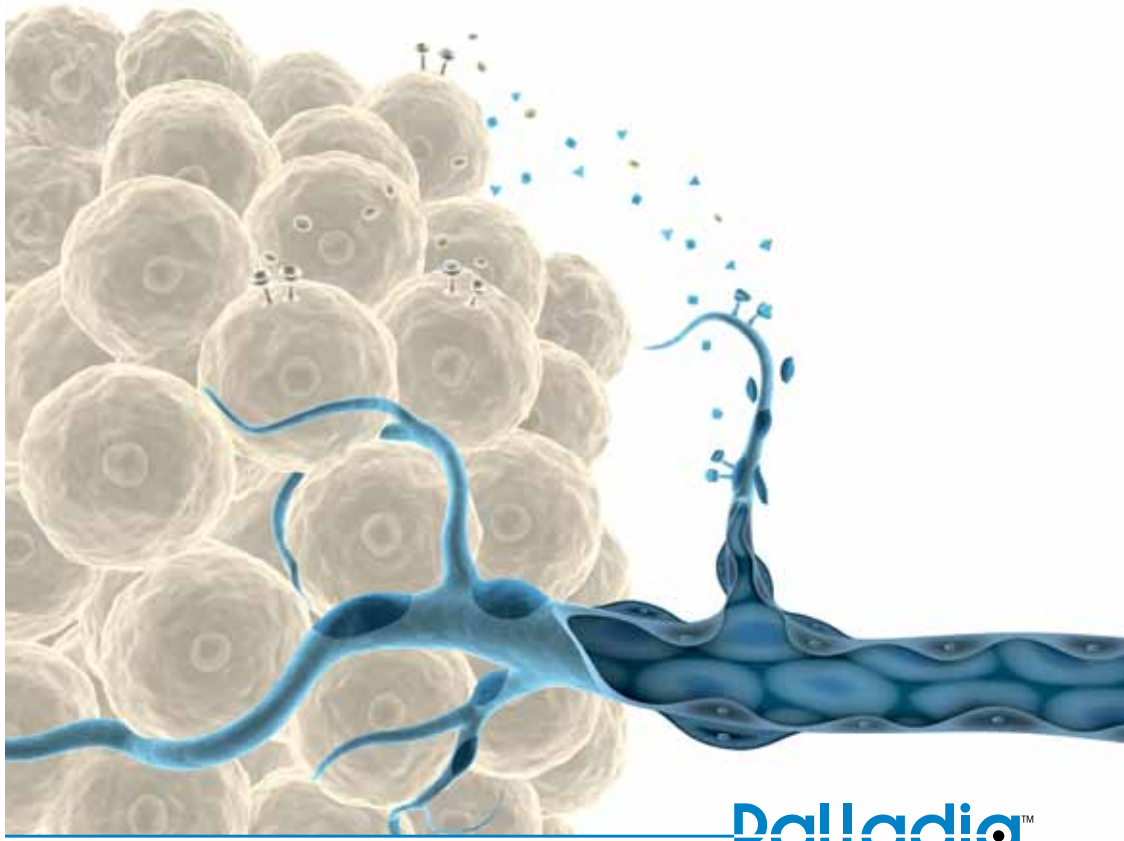
Introducing PALLADIA™:

The first antiangiogenic and antiproliferative cancer treatment developed specifically for the treatment of Mast Cell Tumours in dogs*



Pfizer Animal Health

Palladia™
toceranib phosphate

*Non resectable Patnaik grade II (intermediate grade) or grade III (high grade) recurrent, cutaneous Mast Cell Tumours.

References:

1. London CA et al. Multi-centre, placebo-controlled, double-blind, randomised study of oral toceranib phosphase (SU11654), a receptor tyrosine kinase inhibitor, for the treatment of dogs with recurrent (either local or distant) mast cell tumour following surgical excision. Clinical Cancer Research 2009 15(11):3856-3865.
2. Pfizer Internal Study number 1963C-60-04-688. Pfizer Animal Health.
3. 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. Clin Cancer Res. 2003;9:2755-2768.
4. PALLADIA European SPC and package leaflet

* in the blinded plus the open-label phase of the study
** in the 6-week blinded phase of the study

Pfizer Animal Health

For further information please contact Pfizer Animal Health, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS

Use medicines responsibly (www.noah.co.uk/responsible)
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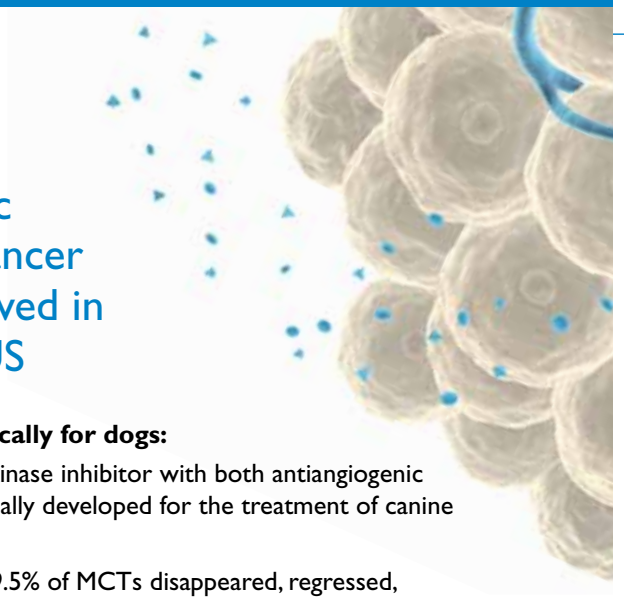

The first antiangiogenic and antiproliferative cancer treatment to be approved in both the EU and the US

PALLADIA was developed specifically for dogs:

- PALLADIA is a receptor tyrosine kinase inhibitor with both antiangiogenic and antiproliferative effects specifically developed for the treatment of canine mast cell tumour (MCT)
- In dogs treated with PALLADIA, 59.5% of MCTs disappeared, regressed, or stabilised[1,2]
  - PALLADIA demonstrated a biological response rate of 59.5%*[1,2]
  - PALLADIA provided a statistically significant improvement in objective response rate vs. placebo[1]
- Health-related quality of life was significantly improved in dogs demonstrating an objective response with PALLADIA (p=0.030)[1]
- Adverse events associated with PALLADIA are generally manageable with dose modification and/or supportive care,[1,3] along with early recognition

PALLADIA administration is convenient for both you and pet owners

- Starting dose 3.25mg/kg orally once every other day
- PALLADIA can be administered by the pet owner at home (for details please read SPC including Special Precautions for people[4])

PALLADIA is an oral selective receptor tyrosine kinase (RTK) inhibitor specifically developed for dogs. It blocks the activity of multiple receptors, resulting in both antiangiogenic and antiproliferative effects.

Pfizer Animal Health

Palladia™ toceranib phosphate

Palladia™ toceranib phosphate Data Sheet

Palladia film-coated tablets for dogs

Presentation

Palladia film-coated tablets for dogs contain 10, 15 or 50 mg toceranib phosphate. Each tablet is round in shape, marked with the Pfizer logo on one side and the strength on the other. The 10 mg tablet is blue, the 15 mg tablet is orange and the 50 mg tablet is red.

Uses

For the treatment of non-resectable Patnaik grade II (intermediate grade) or III (high grade), recurrent, cutaneous mast cell tumours in dogs.

Dosage and administration

For oral use.

Tablets can be administered with or without food.

The initial recommended dose is 3.25 mg/kg bodyweight, administered every second day (see dosing table for details).

The dose given should be based on veterinary assessments conducted weekly for the first six weeks and, thereafter, every six weeks. Duration of treatment depends on the response to treatment.

Treatment should continue in the case of stable disease, or partial or complete response, provided that the product is sufficiently well tolerated. In case of tumour progression, treatment is unlikely to be successful and should be reviewed.

Dosing table:

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 regime.

Dose adjustment/reduction

To manage adverse reactions, the dose may be reduced to 2.75 mg/kg bodyweight or further to 2.25 mg/kg bodyweight administered every second day or treatment can be discontinued for up to two weeks (see Dose Adjustment table below).

Contra-indications, warnings, etc

Do not use in pregnant or lactating bitches or in dogs intended for breeding.

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

Do not use in dogs less than 2 years of age or less than 3 kg bodyweight.

Do not use in dogs with gastrointestinal bleeding.

For any mast cell tumour treatable by surgery, surgery should be the first choice of treatment.

Dogs should be carefully monitored. Dose reductions and/or dose interruptions may be needed to manage adverse events. Treatment should be reviewed weekly for the first six weeks and every six weeks thereafter or at intervals deemed appropriate by the veterinarian. Evaluations should include assessment of clinical signs reported by the pet owner.

To appropriately use the dose adjustment 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.

The safety of Palladia was evaluated in mast cell tumour-bearing dogs with the following:

- Absolute neutrophil count > 1500/microlitre
- Haematocrit > 25%
- Platelet count > 75,000/microlitre
- ALT or AST < 3x upper normal limit
- Bilirubin < 1.25x upper normal limit
- Creatinine < 2.5 mg/dl
- Blood urea nitrogen < 1.5x upper normal limit

Palladia can cause vascular dysfunction which can lead to oedema and thromboembolism, including pulmonary thromboembolism. Discontinue treatment until clinical signs and clinical pathology have normalised. Before performing surgery, discontinue treatment for at least 3 days in order to assure vasculature homeostasis.

If systemic mastocytosis is present, standard pre-emptive care (e.g., H-1 and H-2 blockers) should be implemented prior to initiation of Palladia to avoid or minimize clinically significant mast cell degranulation and subsequent potentially severe systemic side effects.

Palladia has been associated with diarrhoea or gastrointestinal bleeding which may be severe and requires prompt treatment. Dose interruptions and dose reductions may be needed depending upon the severity of clinical signs.

In rare cases, serious and sometimes fatal gastrointestinal complications including gastrointestinal perforation occurred in dogs treated with Palladia. If gastrointestinal ulceration is suspected, whether or not due to Palladia or to mast cell tumour degranulation, stop the administration of Palladia and treat appropriately.

Toceranib is metabolised in the liver and in the absence of any studies on the effects of renal or hepatic impairment, 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 the table overleaf.

Dose adjustment based on clinical signs / pathology	
Clinical signs / pathology	**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 < 2 days or soft stools	Maintain dose level and institute supportive care
> 4 watery stools/day for ≥ 2 days	Discontinue treatment until formed stools and institute supportive care, then 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
Hypoalbuminemia (albumin)	
Albumin < 1.5 g/dl	Discontinue treatment until >1.5 g/dl and clinical signs normal, then decrease dose by 0.5 mg/kg
Neutropenia (neutrophil count)	
> 1000/ul	Maintain dose level
≤ 1000/ul or neutropenic fever or infection	Discontinue treatment until >1000/ul and clinical signs normal, then decrease dose by 0.5 mg/kg
Anaemia (haematocrit)	
> 26%	Maintain dose level
≤ 26%	Discontinue treatment until > 26%, then decrease dose by 0.5 mg/kg
Hepatic toxicity (ALT, AST)	
> 1x – 3x upper normal limit	Maintain dose level; discontinue hepatotoxic drugs, if used
> 3x upper normal limit	Discontinue treatment until ≤3x upper normal limit, discontinue hepatotoxic drugs, if used, then decrease dose by 0.5 mg/kg
Renal toxicity (creatinine)	
<1.25x upper normal limit	Maintain dose level
≥1.25x upper normal limit	Discontinue treatment until < 1.25x upper normal limit, 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.	

* A 0.5 mg/kg dose decrease is a decrease from 3.25 mg/kg to 2.75 mg/kg, or from 2.75 mg/kg to 2.25 mg/kg. The dose should not be < 2.2 mg/kg.

No interaction studies have been performed with toceranib. No information relating to potential cross resistance with other cytostatic products is available.

As toceranib is eliminated to a large extent by metabolism in the liver, the combination with other drugs capable of inducing or inhibiting liver enzymes should be used with caution.

It is not known to what extent toceranib could affect the elimination of other drugs.

Use non-steroidal anti-inflammatory drugs with caution in conjunction with Palladia due to an increased risk of gastrointestinal ulceration or perforation.

Adverse reactions

Results from the clinical field study involving 151 treated and placebo-treated dogs showed that the clinical signs of the disease (mast cell tumour) and treatment-related adverse reactions are very similar in nature.

Very common (more than 1 in 10 animals)

Mild to moderate:

- Diarrhoea, neutropenia, weight loss, blood in faeces/haemorrhagic diarrhoea/gastrointestinal bleeding, anorexia, lethargy, vomiting, lameness/musculoskeletal disorder, dehydration, dermatitis, pruritus, increased alanine aminotransferase, thrombocytopenia, decreased albumin, decreased haematocrit.

Common (more than 1 but less than 10 animals in 100 animals)

Severe:
- Vomiting, diarrhoea, anorexia, lethargy, dehydration, pyrexia, blood in faeces/haemorrhagic diarrhoea/ gastrointestinal bleeding, duodenal ulceration, nausea, septicaemia, skin necrosis, weight loss, increased alanine aminotransferase, decreased haematocrit.

Mild to moderate:

- Localised or general pain, nausea, tachypnoea, polydipsia, flatulence, pyrexia, nasal depigmentation; changes in coat colour, alopecia, urinary tract infection; increased bilirubin, increased creatinine.

Uncommon (more than 1 but less than 10 animals in 1000 animals)

- Severe lameness/musculoskeletal disorder.
- Severe circulatory shock
- There were two deaths that were possibly treatment related. In one dog, pathology findings revealed vascular thrombosis with disseminated intravascular coagulopathy (DIC) and pancreatitis. The other dog died following gastric perforation.
- There were two further deaths; however, relation to treatment could not be established.
- Two dogs developed epistaxis that was not associated with thrombocytopenia. Another dog developed epistaxis with concurrent disseminated intravascular coagulopathy.
- Three dogs had seizure-like activity; however, relation to treatment could not be established.

User warnings:

Palladia may impair male and female fertility and embryo/foetal development. Avoid skin contact with the tablets, faeces, urine, and vomit of treated dogs. The tablets must be administered as a whole and should not be broken or ground. If a broken tablet is rejected by the dog after chewing, it should be disposed of. Wash hands thoroughly with soap and water following handling of the product, and disposing of vomit, urine, or faeces of treated dogs.

Pregnant women should not routinely administer Palladia, should avoid contact with faeces, urine and vomit from treated dogs and broken or moistened Palladia tablets.

Ingestion of Palladia may be harmful for children. Children must not come into contact with the product. Keep children away from faeces, urine or vomit of treated dogs.

Gastrointestinal discomfort such as vomiting or diarrhoea may occur if this drug is accidentally ingested. In the case of accidental ingestion, seek medical advice immediately and show Package Leaflet or label to the physician.

Pharmaceutical precautions

Do not use after the expiry date stated on the carton.

Palladia does not require any special storage conditions.

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

Keep out of the reach and sight of children.

For animal treatment only.

Legal category

UK: POM-V
IE: POM

Packaging quantities

Palladia is available in a cardboard carton containing two child-resistant blister packs, each blister containing 10 tablets.

Further information

Overdosing signs were observed in a toxicity study conducted in healthy adult Beagle dogs treated with 2 mg/kg, 4 mg/kg or 6 mg toceranib/kg once every other day for 13 consecutive weeks without dose interruption. Toceranib was well tolerated at 2 mg/kg dose level whereas adverse reactions were noted in some dogs treated with 4 mg/kg and thus a NOAEL could not be established.

Dogs in the 6 mg/kg every other day group exhibited the most adverse effects which included decreased food consumption and weight loss. Sporadic dose related lameness, stiffness, weakness and pain in limbs resolved without treatment. Anaemia and neutropenia and eosinopenia were dose-related. Two dogs (6 mg/kg) were euthanased at approximately 3 weeks for treatment-related clinical toxicities initiated by decreased feed intake and melaena culminating in anorexia, weight loss and haematochezia.

The main target organs of toxicity include the gastrointestinal tract, bone marrow, gonads and musculoskeletal system.

In case of adverse events following overdose, treatment should be discontinued until resolution and then resumed at the recommended therapeutic dose level.

Marketing authorisation number

EU/2/09/100/001-003