SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Palladia 50 mg film-coated tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each film-coated tablet contains toceranib phosphate equivalent to 50 mg of toceranib.

Excipients:
Titanium dioxide (E171): 0.78 mg
Iron oxide red (E172): 1.73 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Palladia 50 mg: Round shaped, red coloured tablets

Each tablet is marked with the strength (50) on one side, the reverse side is blank.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

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

4.3 Contraindications

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.

4.4 Special warnings for each target species

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

4.5 Special precautions for use

Special precautions for use in animals

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
- Hematocrit >25%
- Platelet count >75,000/microlitre
- ALT or AST <3 X upper normal limit
- Bilirubin <1.25 X upper normal limit
- Creatinine <2.5 mg/dl
- Blood urea nitrogen <1.5 X 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 (See section 4.6).

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 following table.

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 or ≥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/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 (hematocrit)	
>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)	
<1.25 X upper normal limit	Maintain dose level
≥1.25 X upper normal limit	Discontinue treatment until <1.25 X upper normal limit, then decrease dose by 0.5 mg/kg

Concurrent anaemia, azotemia, hypoalbuminemia and hyperphosphatemia
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.

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

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.

Special precautions for the protection of the environment

Not applicable.

Other precautions

Not applicable.

4.6 Adverse reactions (frequency and seriousness)

Dogs:

Very common (>1 animal / 10 animals treated):	Mild to moderate: Diarrhoea, vomiting, blood in faeces, haemorrhagic diarrhoea, digestive tract haemorrhage Anorexia, dehydration, lethargy, weight loss Lameness, musculoskeletal disorder Dermatitis, pruritus Decreased haematocrit, hypoalbuminaemia, elevated alanine aminotransferase (ALT), neutropenia, thrombocytopaenia
Common (1 to 10 animals / 100 animals treated):	Mild to moderate: Localised pain, general pain, polydipsia, pyrexia Depigmentation of the nasal plane, hair coat discolouration, alopecia Nausea, flatulence Tachypnoea Urinary tract infection Elevated total bilirubin, elevated creatinine Severe: Anorexia, dehydration, pyrexia, weight loss, septicaemia, lethargy Diarrhoea, vomiting, blood in faeces, haemorrhagic diarrhoea, digestive tract haemorrhage, duodenal ulcer, nausea Skin necrosis Decreased haematocrit, elevated alanine aminotransferase (ALT)
Uncommon (1 to 10 animals / 1,000 animals treated):	Severe: Lameness, musculoskeletal disorder Circulatory shock

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.

- 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.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

4.7 Use during pregnancy, lactation or lay

Do not use in pregnant or lactating bitches or in dogs intended for breeding (see section 4.3). Other compounds in the anti-angiogenic class of anti-neoplastic 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.

4.8 Interaction with other medicinal products and other forms of interaction

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

As toceranib is likely 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.

4.9 Amount(s) to be administered and administration route

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: PALLADIA TABLETS AT 3.25 MG/KG BODYWEIGHT

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 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 in section 4.5).

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

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 neutropaenia and eosinopaenia were dose-related. Two dogs (6 mg/kg) were euthanised at approximately 3 weeks for treatment-related clinical toxicities initiated by decreased feed intake and melena culminating in anorexia, weight loss and hematochezia.

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. See sections 4.4, 4.5 and 4.9 for Dose Adjustment Guidelines.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic Agents – Other protein kinase inhibitors

ATCvet code: QL01EX90

5.1 Pharmacodynamic properties

Toceranib is a small molecule, multi-kinase inhibitor, that has both direct anti-tumour and anti-angiogenic activity. 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, pathologic angiogenesis, and metastatic progression of cancer. Toceranib inhibited the activity of Flk-1/KDR tyrosine kinase (vascular endothelial growth factor receptor, VEGFR2), platelet-derived growth factor receptor (PDGFR) and stem cell factor receptor (c-Kit) in both biochemical and cellular assays. Toceranib exerts an antiproliferative effect on endothelial cells *in-vitro*. Toceranib induces 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 an activating mutation in c-Kit.

The efficacy and safety of Palladia oral tablets for the treatment of mast cell tumours was evaluated in a randomised, placebo-controlled, double-masked, multicentre clinical field study involving 151 dogs with Patnaik grade II or III, recurrent, cutaneous mast cell tumours with/without local lymph node involvement. The field study comprised a 6-week double-blind placebo-controlled phase followed by an un-blinded phase where all dogs received Palladia for a mean duration of 144 days.

Palladia-treated dogs had a significantly greater objective response rate (37.2 %) compared to dogs treated with placebo (7.9 %). After 6 weeks of treatment, a complete response was noted for 8.1 % and partial response was noted for 29.1 % of dogs treated with Palladia. There was also a significant advantage of Palladia over placebo in the secondary efficacy endpoint, time to tumour progression. Median TTP for Palladia treated dogs was 9 to 10 weeks and for placebo-treated dogs it was 3 weeks.

Dogs carrying wild-type c-kit and dogs carrying mutated c-kit responded significantly better to treatment as compared to placebo.

5.2 Pharmacokinetic particulars

With a regimen of 3.25 mg toceranib/kg bodyweight administered by tablet orally every other day for 2 weeks (7 doses), the following pharmacokinetic parameters of toceranib in plasma in healthy Beagle dogs were reported: elimination half-life ($t_{1/2}$) 17.2 ± 3.9 hours, time to maximum plasma concentration (T_{max}) approximately 6.2 ± 2.6 hours, maximum plasma concentration (C_{max}) approximately 108 ± 41 ng/ml, minimum plasma concentration (C_{min}) 18.7 ± 8.3 ng/ml and the area under the plasma concentration time-curve (AUC_{0-48}) 2640 ± 940 ng·h/ml.
Toceranib is highly protein bound at between 91% and 93%. The absolute bioavailability of toceranib when dosed orally at 3.25 mg/kg was determined to be 86%.

Linear pharmacokinetics were seen irrespective of the route of administration at doses up to 5 mg/kg given twice daily. In an *in-vitro* study, metabolism of toceranib was primarily to the N-oxide derivative in dogs and cats. There are no *in-vivo* data on the hepatic metabolism in dogs. No gender differences in pharmacokinetics were observed *in-vivo*. Following oral administration of toceranib phosphate, approximately 92% of the administered drug is excreted in faeces with another 7% excreted in urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Lactose monohydrate
Cellulose, microcrystalline
Magnesium stearate
Silica, colloidal anhydrous
Crospovidone

Tablet coating:
Macrogol, Titanium dioxide (E171), Lactose monohydrate, Triacetin, Hypromellose, Iron oxide red (E172), Talc.

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

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

6.5 Nature and composition of immediate packaging

Cardboard carton containing four aluminium-PVC child resistant blister packs, each blister containing 5 film-coated tablets.

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

Medicines should not be disposed of via wastewater.

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

7. MARKETING AUTHORISATION HOLDER

Zoetis UK Limited
1st Floor, Birchwood Building
Springfield Drive
Leatherhead
Surrey
KT22 7LP

8. MARKETING AUTHORISATION NUMBER

Vm 42058/5044

9. DATE OF FIRST AUTHORISATION

23 September 2009

10. DATE OF REVISION OF THE TEXT

April 2025

PROHIBITION OF SALE, SUPPLY AND/OR USE

11. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Gavin Hall

Approved: 16 April 2025