PARTICULARS TO APPEAR ON THE OUTER PACKAGE {Cardboard carton}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Palladia 50 mg film-coated tablets

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Each tablet contains 50 mg toceranib (as toceranib phosphate).

3. PACKAGE SIZE

20 tablets.

4. TARGET SPECIES

Dogs

5. INDICATION(S)

6. ROUTES OF ADMINISTRATION

Oral use.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}

9. SPECIAL STORAGE PRECAUTIONS

10. THE WORDS “READ THE PACKAGE LEAFLET BEFORE USE”

Read the package leaflet before use.

11. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

12. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Zoetis UK Limited

14. MARKETING AUTHORISATION NUMBERS

Vm 42058/5044

15. BATCH NUMBER

Lot {number}

16. SPECIAL WARNING(S), IF NECESSARY

If you are pregnant, you should not routinely administer this product; however, if you chose to administer this product, particular care should be taken. Read package leaflet before use.

17. SPECIFIC PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet

18. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

POM-V

Veterinary medicinal product subject to prescription.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS {NATURE/TYPE}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Palladia 50 mg

2. QUANTITATIVE AND QUALITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

50 mg toceranib

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

PARTICULARS TO APPEAR ON THE PACKAGE LEAFLET:

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Palladia 10 mg film-coated tablets for dogs.
Palladia 15 mg film-coated tablets for dogs.
Palladia 50 mg film-coated tablets for dogs.

2. COMPOSITION

Active substance:
Each film-coated tablet contains toceranib phosphate equivalent to 10 mg, 15 mg or 50 mg of toceranib.

Palladia are round film-coated tablets and have a coloured film coat to minimise risk of exposure and to help identify the correct tablet strength.

Palladia 10 mg: blue.
Palladia 15 mg: orange.
Palladia 50 mg: red.

3. TARGET SPECIES

Dogs

4. INDICATIONS FOR USE

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

5. 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 evidence of stomach bleeding. Your veterinarian will advise you if this is the case for your dog.

6. SPECIAL WARNINGS

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

Special precautions for safe use in the target species:
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. Your veterinarian may need to take blood and urine samples from your dog to perform these checks.

- 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 vomit or stools
  - ✓ Unexplained bruising or bleeding
  - ✓ Or if your dog experiences other changes that concern you

Treatment should be permanently discontinued if severe adverse events recur or persist, despite appropriate supportive care and dose reduction.

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

- Children should not come in contact with Palladia. Keep children away from faeces, urine or the vomit of treated dogs.
- If you are pregnant, you should not routinely administer Palladia; however, if you choose to give these tablets to your dog, you should be particularly careful and follow the handling procedures described below.
- If Palladia is accidentally ingested (swallowed or eaten) by you or a family member, seek medical advice immediately. It is important to show the doctor a copy of this package leaflet. In cases of accidental ingestion of Palladia, you may experience stomach discomfort, including vomiting or diarrhoea.

The following handling procedures will help to minimise exposure to the active ingredient in Palladia for you and other members of your household:

- Anyone in your household who administers Palladia to your dog should always wash their hands after handling the tablets.
- When you are handling the tablets:
  - ✓ Do not break or grind the tablets.
  - ✓ Palladia tablets should be given to your dog immediately after they are removed from the blister and should not be left around where they could be handled/swallowed by children.
  - ✓ The blister should always be returned to the cardboard carton once a tablet or tablets have been removed.
  - ✓ If the Palladia tablet is “hidden” in food, make sure that your dog has eaten the entire dose. This will reduce the risk for children or other household members to accidentally come into contact with Palladia.

Pregnancy, lactation and fertility:
Do not use in pregnant or lactating bitches or in dogs intended for breeding (see section 5). 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.

Interaction with other medicinal products and other forms of interaction:
There are some medicines that you should not give to your dog during treatment because together, they might cause serious adverse effects. Tell your veterinarian about all medicines, including over-the-counter products, that you intend to administer to your dog.

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.

Overdose:
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.

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.

7. ADVERSE EVENTS

Dogs:

Very common (>1 animal / 10 animals treated):	Mild to moderate: Diarrhoea, vomiting, blood in faeces, haemorrhagic (bloody) diarrhoea, digestive tract haemorrhage Anorexia, dehydration, lethargy, weight loss Lameness, musculoskeletal disorder Dermatitis (skin inflammation), pruritus (itching) Decreased haematocrit (fraction of red blood cells in the blood), hypoalbuminaemia (low levels of protein in the blood), elevated alanine aminotransferase (ALT) (a liver enzyme), neutropenia (low levels of white blood cells), thrombocytopaenia (low level of platelets)
Common (1 to 10 animals / 100 animals treated):	Mild to moderate: Localised pain, general pain, polydipsia (increased thirst), pyrexia (fever) Depigmentation of the nasal plane, hair coat discolouration, alopecia (hair loss) Nausea, flatulence Tachypnoea (rapid breathing) Urinary tract infection Elevated total bilirubin, elevated creatinine Severe: Anorexia, dehydration, pyrexia (fever), weight loss, septicaemia (blood poisoning), lethargy Diarrhoea, vomiting, blood in faeces, haemorrhagic (bloody) diarrhoea, digestive tract haemorrhage, duodenal ulcer, nausea Skin necrosis (skin flaking and detachment) Decreased haematocrit (fraction of red blood cells in the blood), elevated alanine aminotransferase (ALT) (a liver enzyme)
Uncommon (1 to 10 animals / 1,000 animals treated):	Severe: Lameness, musculoskeletal disorder Circulatory shock

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder or the local representative of the

marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system: {national system details}.

8. DOSAGE FOR EACH SPECIES, ROUTES AND METHOD OF ADMINISTRATION

Oral use.

The initial dose is approximately 3.25 mg/kg bodyweight, given every second day (see dosing table at the end of the printed package leaflet for details).

The number of tablets given to your dog may be adjusted by your veterinarian to manage side effects. Therefore, the dosage given should be as described by your veterinarian, even if this is different from the dosing table.

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: - 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.

9. ADVICE ON CORRECT ADMINISTRATION

Tablets can be administered with or without food.
The tablets must be administered as a whole and should not be divided, broken or ground. If a broken tablet is rejected by the dog after chewing, it should be disposed of. In order to achieve correct dosing, tablets of different strengths (“colours”) might need to be combined as described in the table.
If a dose is missed, the next schedule dose should be given as prescribed. Do not increase or double the dose. If more than the prescribed amount of tablets were given, contact your veterinarian.

Dogs should be carefully observed following administration to ensure that each tablet is swallowed.

10. WITHDRAWAL PERIODS

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
This veterinary medicinal product does not require any special storage conditions.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton after Exp.

12. SPECIAL PRECAUTIONS FOR DISPOSAL

Medicines should not be disposed of via wastewater.

Any unused veterinary medicinal product or waste material derived from such veterinary medicinal products should be disposed of in accordance with local requirements. These measures should help to protect the environment.

Ask your veterinary surgeon how to dispose of medicines no longer required.

13. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

14. MARKETING AUTHORISATION NUMBERS AND PACK SIZES

Vm 42058/5042
Vm 42058/5043
Vm 42058/5044

Cardboard carton containing four aluminium-PVC child resistant blister packs, each blister containing 5 film-coated tablets.
Palladia film-coated tablets are available in 10 mg, 15 mg and 50 mg strength.

15. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED

September 2023

Find more product information by search for the 'Product Information Database' or 'PID' on www.gov.uk.

16. CONTACT DETAILS

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17. OTHER INFORMATION

Special information for the veterinarian

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 < 1.5x 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.

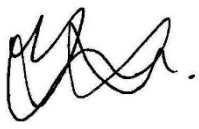
In rare cases, serious and sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred in dogs treated with Palladia. If gastrointestinal ulceration is suspected, whether or not due to Palladia or to mast cell tumour degranulation, stop the administration of Palladia 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 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/ul	Maintain dose level
≤1000/ul 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.



Approved: 07 March 2024