ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

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

Excipients:

Qualitative composition of excipients and other constituents
Tablet core:
Lactose monohydrate
Cellulose, microcrystalline
Magnesium stearate
Silica, colloidal anhydrous
Crospovidone
Tablet coating:
Macrogol
Titanium dioxide (E171)
Lactose monohydrate
Triacetin
Hypromellose
Palladia 10 mg film-coated tablets: Indigo Carmin Lake (E132)
Palladia 15 mg film-coated tablets: Sunset Yellow Lake (E110) Iron oxide red (E172)
Palladia 50 mg film-coated tablets: Iron oxide red (E172) Talc

Palladia 10 mg: Round shaped, blue coloured tablets.
Palladia 15 mg: Round shaped, orange coloured tablets.
Palladia 50 mg: Round shaped, red coloured tablets.

Each tablet is marked with the strength (10, 15 or 50) on one side, the reverse side is blank.

3. CLINICAL INFORMATION

3.1 Target species

Dogs.

3.2 Indications for use for each target species

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

3.3 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 body-weight.
Do not use in dogs with gastrointestinal bleeding.

3.4 Special warnings

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

3.5 Special precautions for use

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. 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 3.6). 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.

3.6 Adverse events

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):	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) 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
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 its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Do not use in pregnant or lactating bitches or in dogs intended for breeding (see section 3.3). 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.

3.8 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.

3.9 Administration routes and dosage

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 3.5).

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

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 3.4, 3.5 and 3.9 for Dose Adjustment Guidelines.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QL01EX90

4.2 Pharmacodynamics

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.

4.3 Pharmacokinetics

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.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

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

5.3 Special precautions for storage

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

5.4 Nature and composition of immediate packaging

Cardboard carton containing 20 film-coated tablets in 4 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.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Zoetis Belgium

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/09/100/001 (10 mg tablets)
EU/2/09/100/002 (15 mg tablets)
EU/2/09/100/003 (50 mg tablets)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 23/09/2009

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

ANNEX II

OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

None.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARDBOARD CARTON/TABLETS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Palladia 10 mg film-coated tablets
Palladia 15 mg film-coated tablets
Palladia 50 mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains 10 mg toceranib (as toceranib phosphate).
Each tablet contains 15 mg toceranib (as toceranib phosphate).
Each tablet contains 50 mg toceranib (as toceranib phosphate).

3. PACKAGE SIZE

20 film-coated tablets.

4. TARGET SPECIES

Dogs.

5. INDICATIONS

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 Belgium

14. MARKETING AUTHORISATION NUMBERS

EU/2/09/100/001
EU/2/09/100/002
EU/2/09/100/003

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Alu-PVC/BLISTERS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Palladia 10 mg
Palladia 15 mg
Palladia 50 mg

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

10 mg toceranib
15 mg toceranib
50 mg toceranib

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

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):	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) 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
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 or household waste.
Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.
Ask your veterinary surgeon or pharmacist 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

EU/2/09/100/001-003

Cardboard carton containing 20 film-coated tablets in 4 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

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

16. Contact details

Marketing authorisation holder:

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Manufacturer responsible for the batch release:

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Local representatives and contact details to report suspected adverse reactions:

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17. Other information

Special information for the veterinarian

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.

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/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.