SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Palladia (as published in October 2009). For information on changes after this date please refer to module 8.

1. SUMMARY OF THE DOSSIER

Mast cell tumours are the most common cutaneous tumours in dogs. It is assumed that the prevalence of mast cell tumours is similar across European member states. Mast cell tumours tend to occur in middle aged to elderly dogs (average of 9 years) and are classified as Grade I (well differentiated), Grade II (intermediate differentiated) or Grade III (poorly differentiated). Mast cell tumours may be (but are not always) a life-threatening condition. The primary disease can sometimes be adequately controlled by surgery and radiotherapy, resulting in less than 20% of the grade II mast cell tumours metastasising.

Although mast cell tumour is one of the major cancer diagnoses in dogs, the total incidence of canine mast cell tumours grade II or III in dogs is very low. Since the overall number of dogs suitable for treatment is expected to be low, the CVMP agreed that the CVMP guidelines on "Minor-Use-Minor-Species (MUMS) data requirements" could be applied when assessing the dossier.

Palladia is an antineoplastic agent for the treatment of mast cell tumours in dogs. The product is presented as film-coated tablets in three different strengths, to be used in different combinations together to achieve accurate bodyweight dependant dosing. For ease of dosing, the tablets have different colours per strength, blue (10 mg), orange (15 mg) and red (50 mg). The active substance is toceranib (in form of toceranib phosphate), a protein-tyrosine kinase inhibitor.

The benefit of Palladia is the anti-tumour effect in Palladia treated dogs as compared to placebo treated, Grade II and III mast cell tumour dog patients. Time to tumour progression in dogs in a late stage of disease is prolonged under Palladia treatment (average of 9-10 weeks) when compared to dogs receiving placebo (average of 3 weeks). Palladia treated dogs showed a significantly greater "objective response" rate (ca 37%) as compared to dogs treated with placebo (ca 8%). After 6 weeks of treatment, complete response was noted for approximately 8% and partial response for approximately 29% of dogs treated with Palladia. No statistical difference was seen in dogs whose tumours contained mutated or normal (wild type) c-kit receptors.

The most common side effects with Palladia are neutropenia, gastrointestinal reactions (diarrhoea), weight loss and difficulties to move (lameness). These reactions are usually mild to moderate and temporary. Dogs under Palladia treatment should be regularly monitored for side effects by the veterinarian (in the beginning of treatment at least once per week). In case of side effects, the veterinarian might decide to lower the dose of Palladia or to discontinue or interrupt treatment.

The approved indication is: "Treatment of non-resectable Patnaik grade II (intermediate grade) or III (high grade), recurrent, cutaneous mast cell tumours in dogs".

2. QUALITY ASSESSMENT

Composition

Palladia film-coated tablets are presented in three strengths, 10, 15 and 50 mg. Palladia contains a new chemical entity, toceranib, as the active substance, which is present in the formulation as the phosphate salt. The finished product contains conventional, pharmaceutical grade excipients and commercial Opadry (hydroxypropylmethylcelluose based) blends are used for film-coating.

The three strengths are differentiated by markings on the tablets and different colours of the film-coat: blue (10 mg); orange (15 mg); and, red (50 mg).

Container

The primary package is a laminated aluminium foil/foil (cold form foil) blister. The pack size is 20 tablets, for all strengths.

Development Pharmaceutics

Manufacture of the tablets utilizes conventional pharmaceutical equipment and follows standard pharmaceutical processing techniques. All strengths of Palladia tablets are manufactured from a common blend by direct compression. The commercial manufacturing process consists of four steps, manufacture of the blend batch, followed by compression, coating and packaging. With the exception of some of the colouring agents in the film coatings all excipients are the subject of a Ph. Eur. monograph. No risk for TSE from any of the ingredients has been identified.

Method of Preparation

The product is manufactured using conventional pharmaceutical equipment and standard processing techniques. There are no critical steps, which require in-process controls, so all the critical parameters are tested at the final product stage.

Active substance

The active substance toceranib phosphate is a crystalline yellow-orange powder with a molecular weight of 494.45 Daltons. It has been shown to be thermodynamically stable and has a uniform appearance. The active substance exists in a single polymorph form (form 1) under all relevant conditions. Evidence of structure has been confirmed by several methods. Its aqueous solubility has been determined as 3.9 mg/ml at room temperature.

Synthesis of the active substance is performed in two steps and starting materials are described. Specification for control of the active substance has been presented.

The active substance is manufactured according to GMP.

Data have been presented for five batches manufactured using the final commercial synthetic route, and six relevant development batches. Validation of all the analytical methods used for control of the active substance has been judged as satisfactory and in compliance with relevant VICH guidelines.

Finished Product

A specification for the tablets has been presented and assessed as satisfactory to control the finished product. The finished product specification includes a test for microbiological quality as well as a test for Uniformity of Dosage units (Ph. Eur. 2.9.40). All the analytical methods used for control of the finished product have been validated, and the validations judged as satisfactory and in compliance with the relevant VICH guidelines.
Batch results for commercial formulation batches have been presented and demonstrate compliance with the finished product specification and consistency of manufacture.

Packaging

Initially, the tablets were to be kept in bottles. However, the packaging was changed from bottles to blisters during the procedure in order to provide a more child-proof packaging.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The ingredients used in the final product comply with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.2) and Commission Directive 1999/104/EEC. No risk for TSE from any of the ingredients has been identified.

Stability

Stability of the active substance was supported by results from four stability batches of toceranib phosphate and stability data have been presented. Based on these data a re-test period of 18 months was justified and accepted. Forced degradation studies on the active substance confirm that the analytical methods used are stability indicating, and that the active substance is not sensitive to light when a dry powder.

Stability tests on the finished product

The packaging was changed from bottles to blisters during the procedure, to provide a more child-proof packaging. Stability data for the product packed in blisters, were presented after storage at 25°C/60%RH, 30°C/65%RH,and 40 °C/75%RH. Six months stability data are available after storage of the tablets in blisters. Long term stability data from storage in bottles up to 18 months are available. The presented data support a shelf-life for the tablets of 1 year in blisters, with no special precautions for storage.

Batches provided were manufactured at the commercial site using the final commercial process at scale.

OVERALL CONCLUSION ON QUALITY

The data provided in Part II is satisfactory and adhere to current guidelines. The composition is adequately described, for ease of use by the animal owner, different tablets strengths are market by different coloured film-coating.

The container is suitable. For user safety reasons, the initial bottle with child-proof closure was later changed into blister presentation.

Adequate information regarding the formulae and packaging of lots used in specific clinical studies have been provided.

The product is manufactured using conventional pharmaceutical equipment and standard processing techniques. There are no critical steps, which require in-process controls, so all the critical parameters are tested at the final product stage.

Satisfactory documentation is presented for the active substance, toceranib phosphate, and for each of the excipients. Satisfactory finished product specifications are provided.

Satisfactory stability studies have been presented and a shelf-life of 1 year has been set.

The applicant has provided a number of post-authorisation commitments.

3. SAFETY ASSESSMENT

Pharmacological Studies
See section 4.1.A Pharmacology.

Single dose toxicity

Oral

Single dose oral toxicity studies were conducted in GLP-compliant studies in the rat at doses from 401 to 3000 mg toceranib/kg bodyweight and in one non-GLP compliant study in the dog at doses from 50 to 500 mg toceranib/kg bodyweight (bw).
In the rat, 2005 mg toceranib/kg bodyweight was a lethal dose, whereas the only finding at the lowest dose (401 mg/kg) was yellow discolouration of the skin and hair.
In the dog, no mortality was observed at doses up to 500 mg/kg bw. In the dog, the gastrointestinal tract was identified as a possible organ of toxicity. Marked emesis and diarrhoea was identified as adverse effects at all dose levels. In addition, increased fibrinogen, platelet counts, and liver enzymes were noted at 500 mg/kg bw. A no observed adverse effect level (NOAEL) of up to 50 mg toceranib/kg bodyweight and a maximum non lethal dose (MNLD) of more than 500 mg/kg bw were suggested for single oral dose toxicity in dogs. However, due to the low number of animals (1) per group, and the lack of post-mortem examination, the dog study was considered as exploratory and can only be used as supportive information.

Dermal

Local tolerance following single dermal application of either toceranib or toceranib phosphate to intact and abraded skin at 500 mg/site was investigated in the rabbit. No mortality or systemic toxicity was observed. Both compounds were found to be non-irritating following single dose exposure, whereas toceranib phosphate was found slightly irritating following repeat dosing at 100 mg/site for 5 consecutive days. These studies cannot be considered as complete single-dose toxicity studies due to the low number of animals (1 male rabbit only in each study) and the lack of post-mortem examination.

The dog appeared to be more sensitive than the rat since gastrointestinal adverse effects were identified already at 50 mg/kg. This finding is of relevance for the User safety. Consequently, User safety following single exposure was evaluated from the results of the repeat-dose toxicity studies.

Repeat dose toxicity

A limited number of repeated dose toxicity studies were conducted in the target species (i.e. the dog) and included a GLP-compliant 13-week margin of safety study, a non-GLP dose-range finding study, and a non-GLP 8-day exploratory study. One non-GLP 2-week oral toxicity study was also conducted in the cat.

In a 13-week oral margin-of-safety study, toceranib phosphate administered once every other day to dogs at 2, 4, and 6 mg/kg bw caused weight loss, decreased food consumption, pancreatic, gonadal, adrenal, muscle-locomotor, and haematopoietic changes with variable dose relationship. Two animals at 6 mg/kg bw were euthanized after 3 to 4 weeks of treatment with additional signs including lymphoid depletion and gastrointestinal effects, progressive anorexia, and weakness. A NOEL was not identified. At the lowest observed adverse effect level (LOAEL) of 2 mg/kg bw/every other day (EOD), effects included slight limb pain and lameness in 1 male, decreased white blood cell counts (much of the decrease was accounted for by a decrease in neutrophils), increased creatine kinase, decreased (8%) mean absolute and relative testes weights, slight to moderate acinar degranulation of the pancreas, minimal cortical congestion/haemorrhage of the adrenal glands, tubular changes in the testes, and reduced incidence of mature/regressing corpora lutea of the ovaries. Systemic exposure was dose proportional and showed no indication of drug accumulation. Also in the preceding dose-range finding study the NOEL following daily oral dosing was below the lowest dose of 2.5 mg/kg bw/day. Due to the exploratory nature and low number of animals/dose, the results of the dose range study and the 8-day exploratory study in the dog are considered as additional supportive information only.

In the 2-week oral toxicity study in the cat, findings at 6.5 mg/kg bw/day included emesis (containing drug and food, frothy, watery), abnormal stools (diarrhoea, soft, mucoid), and reduced body weights and food consumption. Findings at necropsy were limited to 1 female in the 6.5 mg/kg bw/day group with watery colon contents, focus in the duodenum, and red area in the ileum, which correlated microscopically with erosions and haemorrhage in the ileum and degeneration of the superficial mucosa of the caecum and colon. The relevance of this study is limited due to the lack of a vehicle control group and a low number of animals/dose group.

CVMP concluded that a NOEL has not been established in repeat-dose toxicity studies. A repeat-dose toxicity study in the target species only is acceptable for a product intended for use in non food-producing animals. However, the study design of dosing every other day instead of daily dosing was not optimal for a repeat dose toxicity study, unless severe toxicity as a result of drug accumulation precludes daily dosing. In this case there was no clear indication of dose limiting drug accumulation. Nevertheless, the main user safety concern, beside single accidental oral ingestion by a child, is limited to minimal repeat dermal exposure following dosing of the dog every other day and the available data shows that there is no margin of exposure to the established LOAEL of 2 mg/kg bw/EOD. It was therefore concluded that an additional repeat dose oral toxicity study would not add anything to the user safety assessment.

Reproductive toxicity, including teratogenicity

No studies to evaluate effects on reproduction, embryotoxicity, or teratogenicity were conducted. This is acceptable for a product intended for use in non-food producing animals that are not intended to be used for breeding. When considering the pharmacological properties it is agreed that toceranib phosphate should be regarded as reprotoxic, embryotoxic, and teratogenic. Effects on the female and male gonads were also clearly demonstrated in the 13-week oral toxicity study in the dog. Germ cell depletion in the testes, reduction of spermatozoa in the epididymides, and a reduced incidence of mature/regressing corpora lutea were observed from the lowest dose level (2 mg/kg bw/EOD). Reversibility was not investigated and any consequences for female and male fertility are unknown. It should be concluded that toceranib phosphate has the potential to affect male and female fertility with a LOEL of 2 mg/kg bw/EOD, as well as reproduction and foetal development in general without any identified NOEL. This was taken into account in the user safety assessment. In addition, the potential effects on reproduction in the target species, dogs, is reflected in the relevant sections of the SPC.

Mutagenicity and carcinogenicity

The genotoxic potential of toceranib was evaluated in a standard battery of *in vitro* tests and one i*n vivo* test. Toceranib did not induce mutations or chromosome aberrations *in vitro*. Toceranib phosphate was evaluated as positive in one *in vivo* rat bone marrow micronucleus test. A dose-dependent statistically significant increase in micronucleated PCEs as compared to the control was

observed, although this was within historical control values. A second *in vivo* rat bone marrow micronucleus test was conducted and this time no increase in micronucleated PCEs was observed. Based on this finding, in combination with the negative *in vitro* results, CVMP concluded that toceranib phosphate poses no genotoxicity concern. Given the lack of a genotoxicity concern the CVMP considered that carcinogenicity testing was not required.

Studies of other effects

A series of GLP compliant acute dermal irritation and acute ocular irritation studies were conducted in the rabbit using toceranib phosphate or its free base. A local lymph node assay was also performed in the mouse using toceranib phosphate.

Toceranib phosphate was a slight to mild dermal irritant in the rabbit.

A single application of toceranib phosphate was minimally irritating to the eye while multiple instillations caused cumulative irritation which included corneal effects. Rinsing the treated eye with sterile water alleviated corneal effects.

Toceranib phosphate was not a skin sensitizer. There are no studies on irritating and sensitising potential of the final formulation. Instead, a discussion on sensitising and irritating potential of the separate excipients was provided. No evidence for sensitising and irritating potential was available for any of the excipients. When considering the wide use of the excipients in topical formulations (pharmaceuticals and cosmetics), and the low anticipated dermal exposure levels, the final formulation of Palladia is not expected to produce skin irritation or sensitisation. It can be concluded that special warnings regarding irritation and sensitisation is not warranted.

Observations in humans

Toceranib is structurally similar to sunitinib, which is used in human medicines for the indications "Gastrointestinal Stromal Tumour" and "Metastatic Renal Cell Carcinoma" at a dose of 50 mg/day. Sunitinib is known to be cardiotoxic and may induce hypertension in humans.

Studies in humans have not been conducted with toceranib phosphate and the applicant confirmed that toceranib phosphate was never under development as a human medicinal product.

User Safety

A user safety assessment was provided by the Applicant. A number of exposure scenarios were identified, including dermal, ocular, and oral exposure of a veterinarian, pet owner, and a pet owner's toddler to the whole product, traces of product, or product eliminated in excreta and emesis.

There is no margin of safety following acute dermal exposure at 5 mg/kg bw when compared to the non-lethal acute oral dose in the rat assuming 100 % dermal bioavailability and applying an uncertainty factor of 100. Although this exposure scenario was considered highly unlikely, some exposure is likely to occur if the tablets are broken by chewing. Also, when taking repeat exposure from dosing every other day into account there is no margin of safety when comparing 5 mg/kg bw/EOD with the LOAEL value of 2 mg/kg bw/EOD obtained in the 13-week margin of safety study in the dog. However, even if considering a more realistic exposure of 10 % of the dose (0.5 mg/kg bw/EOD) there still is no margin of safety.

In addition, any implications for the user safety regarding male and female fertility, and pregnancy should have been discussed in the light of identified hazards, possible exposure, and established NOEL values. There were no studies to evaluate fertility or embryo/foetal development. Nevertheless,

it can be concluded from the effects on female and male gonads that toceranib has the potential to affect male and female fertility.

Since there is no margin of safety following repeat exposure, effects on male and female fertility cannot be excluded. Toceranib should be regarded as reprotoxic and embryotoxic, however without an established NOEL the margin of safety is difficult to establish. Therefore, effects on embryo/foetal development cannot be excluded following repeat dermal exposure.

It would not be feasible to exclude all fertile men and women, as well as pregnant and nursing women, from handling the tablets or excreta/vomit from treated dogs. Detailed user warnings have, therefore, been included in the SPC and product literature to avoid skin contact with the tablets, excreta or vomit, together with the advice to wash hands. In addition, a warning has been included that Palladia may impair male and female fertility and embryo/foetal development.

The risk of ingestion of the product by children was addressed by the applicant. If one single tablet is orally ingested by a 15-kg child (3.3 mg/kg) the margin of safety is only 1.5 compared to the non-lethal dose to rats when applying appropriate safety factors. However, single dose toxicity was poorly investigated and adverse effects at this exposure level cannot be excluded. In order to reduce the risk of accidental ingestion by children, the applicant changed the packaging from bottles to child-resistant blisters. In addition, special warnings for children have been included in the SPC and package leaflet.

With regard to potential risks following oral/ocular/dermal exposure to emesis and excreta it is agreed that keeping children away from faeces, urine, or vomit of treated dogs is sufficient.

Environmental safety

An Environmental Impact Assessment in accordance with the VICH guideline GL 6 "Guideline on Environmental Impact Assessment (EIA) for Veterinary Medicinal Products – Phase I" (CVMP/VICH/592/98-FINAL) was submitted. Palladia will be used only in non-food producing animals and toceranib is not considered as a DNA-reactive compound having potential for unusual ecotoxicity. Therefore the termination of the EIA at Question 3 in Phase I was considered acceptable without further exposure assessment.
The CVMP concluded that use of Palladia is not likely to pose a risk to the environment.

OVERALL CONCLUSION ON SAFETY

Toceranib is not considered cytotoxic and of low acute toxicity in rats. However, it appears that there are species differences since gastrointestinal adverse effects in the target species (dogs) were seen already at the lowest tested dose level of 50 mg/kg. Toceranib was non-irritating following single dermal exposure to rabbit.

For reproductive toxicity, no specific studies were provided by the applicant. However, effects on the female and male gonads were shown in other studies. Also, it is know that other compounds of this class of antineoplastic agents are known to increase embryolethality and foetal abnormalities. As angiogenesis is a critical component of embryonic and foetal development, inhibition of angiogenesis following administration of Palladia should be expected to result in adverse reactions on the pregnancy in the bitch and a contraindication was included to the SPC and product literature not to use the product in pregnant or lactating bitches or in dogs intended for breeding. Also, reference was made under “Special precautions to be taken by the person administering the veterinary medicinal product to animals” that Palladia may impair male and female fertility and embryo/foetal development and that skin contact should be avoided.

A standard test battery for the assessment of genotoxicity of toceranib was conducted and provided negative results. Based on the absence of any structural alerts, negative mutagenicity findings and the absence of any pre-neoplastic lesions in repeat dose toxicity studies, carcinogenicity studies were not considered necessary.

Toceranib has the potential to affect male and female fertility; however, the product is presented as a film-coated tablet (no contact to the core expected) and detailed user warnings have been included in the SPC and product literature to avoid skin contact with the tablets, excreta or vomit, together with the advice to wash hands. In addition, a warning has been included that Palladia may impair male and female fertility and embryo/foetal development. Special warnings regarding irritation and sensitisation were not considered necessary for Palladia;

Since accidental oral ingestion by a child was considered a potential risk, a child-proof container was considered necessary and particular warnings have been included in the product literature.

The product is intended for use in individual, non-food producing animals only and is not considered as a DNA-reactive compound with potential for unusual ecotoxicity. The risk for the environment was therefore considered low and no further exposure assessment was required.

4. EFFICACY ASSESSMENT

Pharmacodynamics

Information on the pharmacodynamic properties of the receptor tyrosine kinase inhibitor toceranib was provided in form of peer reviewed published literature reports.

Toceranib is a 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 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.

Canine mast cell tumour growth is frequently driven by an activating mutation in c-Kit and about 20 % of the dogs with advanced mast cell tumours carried mutated receptor tyrosine kinase. The dominant form seems to be internal tandem duplication (ITD) in the JM domain of *c-kit*.

Toceranib exerts an antiproliferative effect on endothelial cells *in vitro.* It promoted apoptosis and cell death in two canine and one mouse mast cell lines expressing mutated Kit or mutated Kit together with wild-type Kit, whereas a mouse cell line expressing wild-type Kit only was resistant to the inhibitory effect on cell proliferation except at very high concentration.

These *in-vitro* results indicate that mast cell tumours expressing activating Kit mutations seem to respond more likely to the antiproliferative effects of toceranib than tumours expressing wild-type Kit. However, the clinical data demonstrated that sufficient efficacy is obtained also in wild type c-kit carriers, and other pathways than those explored in these *in vitro* studies may be responsible for the anti-tumoural effect.

Pharmacokinetics

A number of studies on pharmacokinetics of single or multiple doses of toceranib in healthy or patient dogs were provided by the applicant.

Single dose pharmacokinetics and absolute bioavailability were studied in healthy dogs in a two-treatment two-period crossover study with a 14 day washout between treatments. Dogs received either an oral dose of 3.25 mg toceranib/kg bodyweight or an intravenous dose of 1 mg/kg. The bioavailability was estimated to be 86%, indicating good **absorption** although the variability between

samples was fairly high. Food effect on the pharmacokinetics of toceranib was studied after a single oral dose of 3.25 mg/kg in fed and fasted beagle dogs. Plasma samples were obtained from each dog pre-dose and up to 72 hours treatment. No significant differences ($p \geq 0.06$) between feeding states were detected.

Multiple dose data from healthy and patient dogs showed dose proportionality at doses of 0, 2, 4 and 6 mg toceranib/kg over 12 weeks of treatment, and indications of a small amount of drug accumulation. Some data indicated differences in dose proportionality between male and female dog, however, these were not considered to be clinically relevant.

Following administration of an oral dose of 3.25 mg toceranib/kg bodyweight 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 (T_{max}) approximately 108 ± 41 hours, minimum plasma concentration (C_{min}) 18.7 ± 8.3 ng/ml and the area under the plasma concentration time-curve (AUC) 2640 ± 940 hours. The pharmacokinetics after oral administration in patient dogs was similar to that in healthy dogs.

Protein binding was studied *in vitro* and determined to be 90.8-93.1% (mean range). The **metabolism** of toceranib was studied *in vitro*, and one phase I N-oxide metabolite was found.

Excretion was investigated in a mass balance study in dogs receiving a single oral administration of 3.25 mg/kg. Urine, faeces and plasma samples were collected at intervals up to 168 h post dose. The majority (around 90%) of the administered radioactivity was excreted via the faeces whereas urinary excretion accounted for less than 10%. 90% of the radioactivity was excreted by 96 h.

Target Animal Tolerance

Target animal safety was investigated in one pivotal study, supported by four other studies, either to investigate the tolerance (overdose) or in combined dose-finding & tolerance studies.

Tolerance in the dog was explored in a single oral dose study with a 2 week long observation period exposing healthy Beagle dogs to 50, 250 or 500 mg toceranib/kg bodyweight per day. In addition, data were presented from an eight days-long oral exposure study providing test dogs 50 or 300 mg toceranib/kg bodyweight daily and from a combined dose range-finding and tolerance study where between 2.5 and 12.5 mg toceranib /kg bodyweight was provided daily, either once or divided in twice daily doses, or using a 5 days-on-4 days-off-regimen. Also, in a dose-finding study by London and co-workers (2003), safety data were presented. The studies were not GLP-compliant and showed some deficiencies in the study design (e.g. the final formulation was not used, small number of animals). The CVMP therefore considered the results from these studies only as supportive.

However, the studies demonstrated that the gastrointestinal tract (emesis, diarrhoea, appetite reduction, weight loss) is the main target of toxicity for toceranib. Other toxicity signs related to insults to limb function and the lymphatic system bone marrow affection, liver, pancreas and possibly also the kidney. Also, dose ranging studies confirmed that any form of daily dosing regimen is not acceptable from tolerance perspective and the compound was better tolerated if an alternate daily treatment strategy was used.

To explore long term use, data from a 13-week long study was presented where up to 6 mg/kg bodyweight was administered once every other day, according to the proposed SPC.

Only the last study was GLP compliant whereas the four others were not. In the pivotal, GLP compliant 13 weeks-long tolerance study, healthy Beagle dogs, aged 24-27 month-old, weighing 6.2-15.1 kg, received doses of 0 (placebo), 2 mg/kg, 4 mg/kg and 6 mg toceranib/kg bodyweight orally, every other day. Doses were provided at least 1 h after feeding. The following observations were made repeatedly during the study: General health observations, clinical observations, physical examination,

body weight, feed consumption, ophtalmology, ECG, blood sampling for haematology, coagulation characteristics, clinical chemistry and urine analysis. Blood samples for evaluation of systemic exposure was collected at days 0, 28 and 66 (i.e. pre-dosing and 1, 3, 6, 24 and 48 h post dosing). Necropsy was performed of all animals 24h after last treatment.

Two dogs in the highest (6 mg/kg) dose-group were euthanized approximately 3 weeks after start of treatment, due to severe gastrointestinal disturbances mainly dependent on changes in the duodenum and jejunum, leucopenia and anaemia. Signs of liver and renal affection were also noted in one of the euthanized dogs.

In the other dogs included in this study the following toxicity signs were noted: decrease in feed consumption and weight loss, hind limb disorders, neutropenia, anaemia, AST and CK increase, increase in hepatic indices (alkaline phosphatase and LDH) and post mortem changes in gonads, bone-marrow, spleen, pancreas and adrenal gland. The changes were generally dose dependent and occurred in all treatment groups. Thus, a NOAEL was not observed, implying there is no safety margin for the proposed dose levels. Since the proposed dose is evidently above any safety margin, CVMP accepted that higher doses were not tested (3 x and 5 x the suggested dose, as normally required).

All safety investigations were undertaken in mature dogs. Since tolerance has not been established in younger animals, a contraindication is included in the SPC and package leaflet that dogs of less than 2 years of age should not be treated.

Toceranib is structural similar to sunitinib, which is used in human medicine, where it is known to be cardiotoxic and may induce hypertension in humans. The applicant was requested to discuss any potential cardio-toxic effects of toceranib in dogs. No potential cardio-toxic effects or hypertension were observed in dogs treated with toceranib.

Dose Determination

Dose Finding

Daily versus alternate dosing:
In the identification of an appropriate dose, the applicant took into account a study investigating the possible benefit of a twice daily treatment regimen instead of a once daily regimen; or a once daily treatment for 5-day periods separated by a 4 day-long recovery phase, explored with different daily doses (2.5-12.5mg/kg bw). The toxicity pattern was similar to the other studies (emesis, diarrhoea, appetite reduction, weight loss and bone marrow affection*)*. A dose relationship was only slightly indicated and clear toxicity signs were noted also in the lowest dose group which is within the suggested dose range (2.2-3.25 mg/kg bodyweight). The applicant came to the conclusion that any form of daily dosing regimen is not acceptable from tolerance perspective.

This finding was confirmed in the study by London and co-workers (2003) where doses above 2.5 mg/kg bodyweight could not be administered for safety reason when the test item was provided on a daily basis, whereas higher doses were better tolerated if an alternate daily treatment strategy was used. This study further confirmed that the gastrointestinal tract is the main target of toxicity but also indicated effects on bone marrow function and limb function. In that study, one dog receiving 5 mg/kg bodyweight was euthanized due to gastrointestinal bleeding.

Proposed starting dose
The proposed starting dose of 3.25 mg toceranib/kg bodyweight was based on a peer reviewed publication by Pryer and co-workers (2003) concerning clinical patients with Grade II/III mast cell tumours (MCT). Eight hours after treatment, a more than 50 % reduction in phosphorylated KIT from biopsy tissue as compared to baseline values was noted in 73 % of the treated animals. Among responders, plasma concentrations of active substance at that time (8 hours post dosing) was 33 - 121 ng/ml, and among non-responders it was 95 -158 ng/ml. Among carriers of mutated c-kit, response

rate seemed higher compared to Wild-type carriers, although the author claimed that inhibition correlated more closely to baseline Kit phosphorylation.

In addition, exposure at the proposed dosing schedule is presented from a pharmacokinetic study where in total 7 alternate daily doses of 3.25 mg/kg bodyweight were investigated. The C_{min} range for the first and seventh dose was 4.7-25.4 ng/ml and 8.6-35.1 ng/ml, respectively. Corresponding C_{max} ranges were 62-135 ng/ml and 62.7-203 ng/ml, respectively. Mean t½ for the first and seventh dose were 16.4(±3.6) h and 17.2(±3.9) h (t½ for dose seven regards 8-48 hr), respectively. The study demonstrates that accumulation is minimal and that by use of the proposed starting dose, exposure will reach the range found to be connected to response in the work by Pryer and co-workers.

Other observations
Pharmacokinetic data collected from a few patient dogs in the pivotal field study demonstrated a similar exposure pattern as noted in healthy Beagle dogs provided a similar dose. Furthermore, exposure level seemed to correspond to the concentrations proven to provide sufficient inhibition of RTK. Results from a pharmacokinetic study confirmed that exposure is similar in fed and in fasted animals, therefore no recommendations regarding dosing in relation to feeding would be needed.

Resistance

In response to a question from CVMP regarding the potential for resistance development against tyrosine kinase inhibitors, the applicant responded that no specific data for Palladia are available but on basis of data from similar substances approved for use in humans, development of resistance could be expected. CVMP accepted the lack of specific data for Palladia since treatment success is closely monitored by the veterinarian and in case of tumour progression, the need to continue treatment would be reviewed, as indicated in the SPC.

OVERALL CONCLUSION ON THE PRECLINICAL PART

Palladia is a tyrosine kinase inhibitor which *in vitro* selectively inhibits the c-Kit tyrosine kinase receptor (the mast cell growth factor receptor) with a high affinity for a mutated form of c-Kit and to a lesser extent c-Kit Wildtype (WT). Studies on secondary pharmacodynamics included potential effects on cardiac function, respiratory functions and central nervous system; however, no such adverse effects could be found in dogs.

Following oral administration, toceranib is rapidly absorbed. No accumulation is expected using the treatment dose and toceranib is moderately rapidly excreted (within 48 hours), mainly as parent compound via faeces. A number of metabolites have been identified; however, no data on the pharmacological activity of these are available. Toceranib binds to a high degree to plasma proteins and inhibits different isoforms of human cytochromes P450 isoforms, indicating the possibility of drug-drug interactions.

Dose dependent and dosing interval-dependent toxicity signs were demonstrated mainly in the gastrointestinal tract but also in several other organs and functions, such as bone marrow, liver, kidney, gonads, pancreas, adrenal glands and locomotory function. These signs occur at doses above but also within the suggested therapeutic range implying the suggested dose range has no safety margin. Safety data suggests that an alternate daily dosing strategy is better tolerated than daily dosing.

By use of the suggested starting dose of 3.25 mg/kg, phosphorylation was inhibited in MCT patient tissue to a set target level for a high proportion (73 %) of the dogs. Furthermore, objective response or disease stabilization of more than 10 weeks was noted in 59 % of MCT patients treated with doses of 1.25 mg/kg to 3.75 mg/kg either daily or every other day. For different kinds of malignancies the proposed dose range (2.2 mg/kg - 3.25 mg/kg bodyweight) covering the recommended starting dose and the lowest dose recommended in case of adverse events, seems connected to a similar response

rate and the proposed dose level gained further support in the pivotal clinical efficacy study. The studies cited to support the recommended dose indicated that KIT-status (mutated or Wild-type) influences response.

Clinical Studies

Clinical efficacy and tolerance of toceranib were demonstrated in a study by London and co-workers (2003) and by a pivotal field study.

London and co-workers (2003) investigated in a single armed, open-label study efficacy and safety in escalating doses of 1.25, 2.5, 3.25 and 3.75 mg toceranib/kg bw, using different dosing schedules: daily, alternate daily (EOD) or in a 7-days loading dose followed by alternate daily maintenance therapy. Treatment was given in 3-week cycles over a maximum time of 76 weeks. Patients were allowed concomitant treatment with other medicines.

The study included dogs with spontaneous tumours of different forms, including dogs with mast cell tumours. Dogs included in the study had a life expectancy of at least 6 weeks and adequate organ functions, and a median age of 10 years (range 2-14 years). Dogs were evaluated at baseline and for toxicity at day 7, day 21 and then every 3 weeks based on the National Cancer Institute Common Toxicity Criteria adapted for use in dogs (grading of adverse event severity in 5 grades). Efficacy endpoints investigated were the Objective response (OR), including partial or complete response, or stable disease (SD); time to tumour progression (TTP) and the overall survival (OS).

Tolerance:
On the alternate daily dosing regimen (EOD), drug related toxicities were of a more limited magnitude (Grade 1-2) than on the daily treatment regimen (Grade1-3), and often readily amenable to supportive care whereas in the daily treatment group toxicity signs often remained despite supportive care. One dog on 5 mg/kg was euthanized due to gastrointestinal bleeding. Adverse reactions mainly concerned the gastrointestinal tract (diarrhoea, anorexia, vomiting), but also fatigue, hind limb weakness and changes in blood parameters (neutropenia, thrombocytopenia, anaemia, and an increase in urea, creatinine and ALT). The changes were most often mild to moderate. Hind limb weakness connected to signs of muscle pain was commonly noted. Myositis was a suspected cause but this was not confirmed. The results confirmed that a daily administration was connected to unacceptable toxicity and that, from a safety perspective, alternate daily dosing (EOD) is to be preferred to a daily dosing strategy.

Efficacy
For all type of tumours included in the study a dose dependent pattern for OR/SD was noted (response rate at 1.5 mg/kg was 28%; 2.5 mg/kg: 58%; 3.25 mg/kg: 55% and at 3.75 mg/kg: 75%). However, group sizes were small and MCT patients were not investigated separately in view of a possible dose response relationship.

Objective response (OR) or disease stabilization (SD) for more than 10 weeks was noted in 59 % of MCT dogs. Mutated c-kit seems to highly influence response rate; among mutated carriers response rate was 91 %, whereas among Wild-type carriers it was 27 %. Response was also significantly lower among patients with lymphatic involvement. No dog with lymphatic involvement and carrying Wild type KIT responded to treatment, whereas response was 100% among carriers of mutated c-kit without lymph node involvement.
Time to tumour progression (TTP) was 21 weeks for mutated carriers and 3.9 weeks for Wild-type carriers ($p=0.05$), and Overall survival was 36.9 weeks and 15.4 weeks for mutated and Wild-type carriers, respectively ($p=0.12$).
However, the difference in response noted in this study between Wild-type and mutated c-kit carriers was not confirmed by the pivotal clinical study. In this study, a significant effect of treatment was noted for both, mutated as well as Wild-type carriers and, thus, CVMP concluded that Palladia could be used independently of c-kit status.

The **pivotal clinical study** was a GCP-compliant placebo-controlled double-blinded, randomised field study conducted in 2003-2005 at several locations in the USA.

The study included dogs of various age groups (3-15 years), gender and breed with recurrent mast cell tumours (grade II or III) with and without lymph node involvement. The study was conducted in two phases:
In phase 1 (blinded phase over 6 weeks), dogs were randomly allocated to either Palladia or placebo treatment. Cases that progressed after 3 weeks or 6 weeks were un-blinded; only placebo animals were then allowed to shift to Palladia treatment (for the extended study), whereas dogs already on active treatment had to terminate the study. After 6 weeks (Phase 1), the extended, unblinded treatment (Phase 2) started lasting on average 143 days (range 2-812 days). All dogs from phase 1 (Palladia and placebo) with stable disease (SD), partial response (PR) or complete response (CR) were permitted in this open-label phase and all dogs received treatment with Palladia. Animals were monitored by a veterinarian at 3 and 6 weeks, then every 6 weeks.

Treatment started with the recommended dose of 3.25 mg/kg (EOD); however, dose reductions in 0.5 mg/kg steps to a minimum of 2.25 mg/kg bw, and drug holidays (maximum 2 weeks) were made on the basis of toxicity at any point throughout the study. For the extended study phase, where no placebo group was included, the following efficacy results were noted; Objective response (OR) or Stable Disease (SD) for more than 10 weeks was 59.5 %, Time to Tumour Progression (TTP) was 11.9 weeks and duration of response was 12 weeks. Since there is no comparison group, the clinical importance of these findings could not be determined.

Objective response rate
The primary efficacy endpoint during the blinded study phase chosen by the applicant was "Objective response rate" (OR). OR was significantly higher in the Palladia group (37.2 %) than in the placebo group (7.9 %), ($p<0.001$). Among the responders in the Palladia group, 78 % showed a partial response and only 22 % a complete response.

Response rate (OR) seemed not to be influenced by tumour Grade, lymph node involvement or prior anticancer therapy ($p>0.05$). Also, Kit-status (mutated or Wild-type) did not significantly influence the objective response of Palladia treated dogs as compared to placebo.

In all dogs (i.e. Palladia and placebo groups combined), OR was significantly increased by treatment with the test product in both, mutated and wild type carriers (60% and 31.3%, respectively).

The percentage of dogs carrying mutated c-kit was 19 %. However, in response to CVMP's concern regarding potential lack of efficacy for wild type c-kit carriers the applicant compared odds ratios (Palladia vs. placebo) separately for wild type and mutated c-kit carriers. Although the odds ratio for c-kit negative dogs was smaller (5.22) than for c-kit positive dogs (12.60), significant differences as compared to placebo were noted for both sub-populations ($p<0.03$). Also, dogs that had received at least one dose of Palladia, showed no significant difference with regard to median TTP between c-kit negative (10.9 weeks) and c-kit positive (12.9 weeks) dogs.

The CVMP, therefore, concluded that Palladia treatment was effective in both populations, dogs carrying Wildtype or mutated c-Kit, and that no differentiation in the SPC or product literature was necessary when treating these dogs with Palladia.

Time-to-Tumour Progression
A statistically significant difference in Time-to-Tumour progression (TTP) was demonstrated at the end of the initial 6-week blinded phase which showed that for the placebo group median TTP was only 3 weeks whereas for the Palladia group it was 9 to 10 weeks. The Committee noted the relatively modest time periods but acknowledged that the dogs in the study were in an advanced stage of disease as indicated by the rapid disease progression and other clinical signs (e.g. lymph node involvement).

Tolerance
During the initial, 3 to 6 week-long blinded study phase, adverse events occurred significantly more frequent in the Palladia group (94.3 %) than in the placebo group (79.7 %), but severe events (Grade 3 and 4 on a 4-graded scale) were equally common in both groups (placebo group: 15.6%; Palladia group: 20.7%). Gastrointestinal events, loss of weight and condition and neutropenia occurred more commonly in the Palladia group as compared to the control group. The incidence of lameness and musculoskeletal disorders did not differ significantly between the two groups although figures were numerically higher in the Palladia group. Neutrophil decrease was more common in the Palladia group, whereas there were no other significant differences in clinical pathology or serum chemistry parameters between groups during this period. Supportive treatment was somewhat higher in the Palladia group (72 %) than in the placebo group (64 %). Health related quality of life (HRQL) was equal in both group .

In the second, combined blinded and extended study phase adverse event were reported in a similar proportion of treated animals (95.2 %) as in the blinded phase and severe events (Grade 3 or 4) were very common (34.5 %). Gastrointestinal signs dominated (diarrhoea: 59 %, Emesis/vomiting: 48 %) but common findings were also anorexia (50 %), lethargy (39 %), neutropenia (31 %) and lameness (22 %). Digestive tract haemorrhage was noted in 13 % of dogs and haemorrhagic diarrhoea in 8 % of dogs. Weight loss was noted in all animals during this phase of the study (range: -1.7 kg to -12.7 kg).

Two deaths occurred in the Palladia treated group (Day 92 and 221). Gastric perforation was confirmed in one dog. In the placebo group 3 deaths occurred (Day 2 and 7 after the end of the blinded phase when these dogs had been shifted to Palladia treatment). For the dog which had been on Palladia treatment for 7 days, death is regarded as being possibly related to treatment.

Clinical pathology-related toxicities was dominated by neutrophil decrease (44.8 %) but a decrease in albumin, platelets and hematocrit was quite common, as were an increase in ALT, creatinine and bilirubin. Severe changes (Grade 3 or 4) were noted in some dogs regarding each of these parameters.

The reason for the occurrence of locomotor disorders could not be established and a possible treatment relationship has not been ruled out, which has been reflected in the SPC.

Quality of life
Health related quality of life (HRQL) assessment was performed by the animal owner at the end of the initial, blinded phase (i.e. 6 weeks) and based on the owners´ judgment, put into scores, on how the dog performed and coped in its everyday life. Quality of life remained unchanged under treatment with Palladia. Adverse events occurred more frequently in the Palladia group but severity was nearly the same in both groups (placebo and Palladia). Most of the occurring adverse events seem to be manageable using supportive medication and the use of such supportive medication was similar in placebo and the treatment group.

The Committee noted also that most of the adverse reactions would reflect the clinical signs associated with the underlying disease (mast cell tumours), as indicated by the high amount of adverse reactions in placebo dogs. In addition, it is known that any medical treatment of mast cell tumours, independent from the compound used, would result in the release of heparin and histamine, causing adverse reactions in the patient. The majority of adverse reactions associated with Palladia treatment are likely to be controlled by concomitant treatment of e.g. antiemetics, as required. In addition, recommendations are made in the SPC and package leaflet to advise the veterinarian to reduce the dose or to (temporarily) interrupt treatment.

The CVMP, therefore, concluded that the quality of life of dogs is unlikely to deteriorate under treatment with Palladia.

OVERALL CONCLUSION ON EFFICACY

Two clinical studies were provided, demonstrating that Palladia has antitumoural properties in dogs, indicated by tumour shrinkage or stabilisation of tumour growth (OR+SD) in 37-59 % of dog patients with mast cell tumours (grade II or III).

In the pivotal study the applicant selected OR rate assessed during 6 weeks of treatment as primary efficacy endpoint and a significant effect as compared to placebo is demonstrated. The choice of primary endpoint chosen by the applicant (OR) was different to the recommendations expressed in the CVMP "Guideline on Dossier requirements for anticancer medicinal products for dogs and cats" (EMEA/CVMP/28510/08), which recommends TTP as primary endpoint; however, the CVMP acknowledged that the guideline was only developed after the clinical trials had already been started.

However, since efficacy cannot be supported solely by OR comparisons the provision of TTP data was considered essential for a final conclusion and the applicant demonstrated a significant prolongation of time to progression for Palladia treated dogs (9-10 weeks) as compared to placebo treated dogs (3 weeks). The difference in weeks between the Palladia and the placebo group is quite modest. It is accepted however that effect difference may be small due to the fact the dogs were in late stage of disease and study design did not allow for a thorough assessment of long-term effects.

Pharmacodynamic data and dose finding data suggested that KIT-status (mutated or Wild-type) would influence treatment outcome to a significant extent and that treatment response might be inferior for Wild-type carriers. Although it appears that the mutated c-kit carriers might respond better to treatment, the data provided by the applicant in response to this concern showed that a sufficient effect is obtained also for wild type carriers and that no differentiation of kit-carriers in the SPC or product literature was necessary when treating these dogs with Palladia.

The safety data demonstrates that adverse events concerning mainly the gastrointestinal tract, leading to vomiting, diarrhoea and weight loss, are more common among Palladia treated animals than placebo and deaths due to gastrointestinal injuries may occur. Furthermore, effect on the function of bone marrow, kidneys, liver, and the locomotor apparatus is indicated. Almost all dogs (95.2 %) on Palladia treatment on a longer term basis (extended study phase) suffer some kind of adverse event and a high proportion of these dogs (34.5 %) suffer severe events. Supportive treatment seems required for Palladia treated animals to an extent at least as high as for placebo treated animals. The applicant clarified that no difference in demand for supportive treatment should be expected since release of histamine is associated to tumour response and thus treatment to control the potential adverse effect on the gastrointestinal tract is needed. From the quality of life data presented it appears that life quality was neither positively nor negatively affected by treatment.

5. BENEFIT RISK ASSESSMENT

Palladia is an innovative veterinary medicinal product containing toceranib as the active ingredient, a protein-tyrosine kinase inhibitor. Palladia is indicated for the treatment of non-resectable Patnaik grade II or III, recurrent, cutaneous mast cell tumours in dogs. The CVMP confirmed that for this type of application (oncology product), the CVMP guidelines on "Minor-Use-Minor-Species (MUMS) data requirements" could be applied.

BENEFIT ASSESSMENT

Direct benefits

Palladia is of value in the treatment of canine mast cell tumours as demonstrated by the anti-tumour effect (Objective Response) in Palladia treated versus placebo treated Grade II and III mast cell tumour dog patients. The response was mainly partial and a complete response was seen more rarely.

Time to tumour progression is prolonged in dogs in a late stage of disease, to a quite modest but significant extent for Palladia treated animals in comparison to placebo dogs.

Although a better effect of treatment might occur in dogs carrying mutated c-kit, a significant effect of treatment is also demonstrated for wild-type c-kit carriers.

From the quality of life data presented it appears that life quality was neither positively nor negatively affected by treatment.

RISK ASSESSMENT

The main potential risk identified for Palladia concern the tolerance in the target animal.

There is no safety margin for the suggested starting dose and thus Palladia treatment is connected to a significant increase in adverse events as compared to placebo although clinical data suggests that there is no difference in the incidence of the most severe adverse events.

The adverse events concern mainly the gastrointestinal tract but also several other organs and functions. Treated animals would typically suffer from diarrhoea and vomiting episodes, weight loss and reduced appetite. The adverse signs of treatment resemble to large extent the disease signs which make the evaluation of treatment-related adverse events more difficult.

Severe adverse events are commonly noted during treatment on long term basis and deaths due to gastrointestinal insults may occur at rare occasions.

Supportive treatment is required to a similar extent for Palladia treated animals and placebo animals.

Evaluation of the benefit risk balance

Significant effects of treatment in terms of tumour response and postponement of tumour progression have been demonstrated. However, very few animals had a complete response to treatment and, with regard to postponement of disease progression, the difference in weeks between the Palladia and the placebo group is quite modest and the study design did not allow for a thorough assessment of long-term effects.

It is likely that a better effect of treatment will be noted in dogs carrying mutated c-kit as compared to wild-type carriers. Nevertheless, it appears a significant effect of treatment could be expected also for wild-type c-kit carriers and no differentiation in c-kit carriers is necessary in the SPC and package leaflet.

Adverse events are more common among Palladia treated dogs, although there is no increase in more severe events. From the quality of life data presented it appears that life quality was neither positively nor negatively affected by treatment. A reduced demand for supportive treatment should not be expected since adverse events occurring in response to treatment needs to be controlled to maintain life quality.

Conclusions

The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.

Based on the original and complementary data presented, the CVMP concluded that the quality, safety and efficacy of Palladia were considered to be in accordance with the requirements of Directive 2001/82/EC, as amended.