

What you need to know about Palladia (toceranib phosphate)

Pfizer recently received FDA approval for a novel drug, Palladia that is indicated for the treatment of mast cell tumors in dogs. The release of Palladia has generated a significant amount of excitement as not only is it a novel drug for the treatment of mast cell tumors but it represents a new era in veterinary oncology. Palladia will be available only through veterinary oncologists and selected specialists until at least December of 2009. During this time Pfizer will continue to gather data in regards to the safety and efficacy of Palladia. Therefore in order for a patient to receive treatment with Palladia, they must be referred to a veterinary oncologist or participating specialist.

How does Palladia work?

Palladia is in a family of drugs called receptor tyrosine kinase (RTK) inhibitors. In a normal cell, cellular growth and proliferation is tightly controlled by RTK's that are found on the cytoplasmic or nuclear membrane of the cell. In malignant cells, there are mutations that cause these RTK's to be constitutively activated, leading to unregulated growth of these cells. In human oncology, there are already 15 or more drugs that can inhibit RTK's with over 50 more in development.

Palladia is a small molecule that fits into the receptor site of certain RTK's and then blocks kinase activation. Kit is a receptor that is found on the surface of mast cells and C-kit, the gene for this receptor, has been shown to be mutated in 20-30% of all mast cell tumors. Dogs with tumors that have this mutation are known to have a poorer prognosis. Palladia has been developed to be a specific inhibitor of kit. Palladia has also been shown to inhibit both PDGF and VEGF receptors which means that it is likely to also have anti-angiogenic activity.

How effective is Palladia?

A Phase III trial had been conducted using Palladia for the treatment of dogs with measurable Grade II or III mast cell tumors. Dogs were randomized to receive either Palladia or a placebo. In those dogs that received Palladia, the combined response rate (complete and partial response rates) was 37.2%. Dogs that had progressive disease on the placebo were then allowed to receive Palladia and when this group of dogs was included, the overall combined response rate was 42.8%. Dogs with c-kit mutations and no lymph node metastasis were more likely to have a response to Palladia. For those dogs that had an objective response, the duration of the response was 12 weeks. Dogs with Grade II mast cell tumors were more likely to have a longer response. It was also found that about 12% of the dogs had stable disease. When combined with the objective response rate, it means that Palladia has almost a 60% biologic response rate.

What are the side effects of Palladia?

Although Palladia is not a chemotherapeutic, side effects can be similar. The most common side effect was gastrointestinal toxicity which included diarrhea, bloody diarrhea, loss of appetite, vomiting and weight loss. It is important to address these side effects immediately as dogs that were not promptly treated went on to develop more serious clinical signs. The most commonly used drugs to manage these side effects were famotidine, omeprazole, metronidazole, loperamide, sulfasalazine, metoclopramide and

Cerenia. For those dogs with more significant side effects, dose reductions and temporary cessation of treatment for up to 2 weeks was required.

Dogs that had pre-existing gastrointestinal symptoms due to mast cell disease were significantly more likely to develop GI toxicity. At this time NSAIDs are not recommended for dogs receiving Palladia due to the increased risk of gastrointestinal ulceration. Palladia also causes neutropenia although the neutropenia did not require any dose reductions or treatment delays. Lameness and muscle cramping were observed in a small percentage of dogs although this resolved and did not recur.

Can Palladia be used in combination with chemotherapy?

Ultimately it is hoped that Palladia can be used with chemotherapy but for the present time this is not recommended given the overlapping spectrum of side effects. Prednisone can be used concurrently with Palladia. Chemotherapy can be given first to decrease the volume of disease so that dogs may be less susceptible to gastrointestinal side effects of Palladia.

What Patients will benefit from Palladia?

Palladia is currently licensed for the treatment of Grade II and III, recurrent, cutaneous mast cell tumors in dogs with or without nodal involvement. Palladia is an option for the same patients for whom chemotherapy is indicated. This would include dogs with non-resectable mast cell tumors, dogs with regional or systemic disease and possibly dogs with multiple or recurrent mast cell tumors (if surgery +/- radiation therapy is not an option).

Palladia can also be considered as an adjuvant therapy (following surgery +/- radiation therapy) for those dogs that have negative prognostic factors including the following: Grade III tumors, tumors with high mitotic index, tumors with c-kit mutations, large tumors or tumors with a rapid growth rate or tumors in a negative location (inguinal region). There is no data available yet in regards to the efficacy of Palladia as an adjuvant therapy.

Although Palladia was more effective in dogs that had c-kit mutations, it is not felt that testing for c-kit mutations is necessary prior to treatment.

Palladia is NOT indicated as a first line therapy for those mast cell tumors that can be effectively managed with surgery with or without adjuvant radiation therapy. For those dogs where this is not an option, the current recommendation is to use Palladia after the standard chemotherapy options have been exhausted.

There is currently no information regarding the safety and efficacy of Palladia in cats and is therefore not recommended for this species.

How is Palladia administered?

Palladia is an oral drug given every other day at home. The drug can be given either with or without food. The drug comes in 10, 15 and 50 mg tablets. Dosages are either rounded up or down to prevent the need to split tablets. The current recommended follow-up is weekly visits with CBC's for the first 6 weeks and then follow-up visits with a CBC every 6-8 weeks. Most dogs that developed side effects did so in the first 6 weeks and were less likely to have problems thereafter. A chemistry profile should be obtained as a baseline and then every 4-8 weeks to monitor renal values and protein levels.

How should Palladia be handled?

Standard precautions should be taken when handling the drugs including not crushing or splitting the tablets, washing hands well after handling the drugs and/or wearing gloves and not allowing children or women who are pregnant to handle the drug. Care should also be taken to avoid contact with urine, feces or vomitus from treated dogs.

Are there other cancers for which Palladia may be effective?

The main action of Palladia in mast cell tumors is through the inhibition of kit which is found most commonly on mast cells although both gastrointestinal stromal tumors (GIST) and plasma cells have kit receptors. Palladia may be an option in the treatment of GIST and multiple myeloma. Given that Palladia also inhibits PDGR and VEGF, it is possible that Palladia will be effective as an anti-angiogenic agent in other cancers. In the initial Phase I clinical trial, Palladia also had effect against mixed mammary gland carcinomas, soft tissue sarcomas and multiple myeloma. Another potential tumor candidate would be melanoma.