

Toceranib Phosphate

- **(toe-ser-a-nib)**
- ***Palladia*®**
- **Tyrosine Kinase Inhibitor Antineoplastic**

PRESCRIBER HIGHLIGHTS

- Tyrosine kinase inhibitor FDA-approved for grades II or III canine mast cell tumors.
- Most common adverse effects are: diarrhea, decreased/loss of appetite, lameness, weight loss and blood in the stool.
- Adverse effects can be serious and require treatment pause or dose reduction.
- Monitoring essential.

USES/INDICATIONS

Toceranib is indicated for the treatment of Patnaik grade II or III, recurrent, cutaneous mast cell tumors with or without regional lymph node involvement in dogs.

Toceranib may prove useful for treating a variety of tumors in dogs, including sarcomas, carcinomas, melanomas, and myeloma. Toceranib as part of metronomic therapy (using low doses of chemotherapy) and/or combined with radiation therapy, and in combination with other anti-cancer agents such as vinblastine (Robat *et al.* 2012), cyclophosphamide (Mitchell *et al.* 2012), carboplatin (de Vos *et al.* 2012), lomustine (CCNU), piroxicam (Chon *et al.* 2012), prednisone, and calcitriol (Malone *et al.* 2010) are being investigated.

Preliminary data suggest that toceranib may have biological activity against feline squamous cell carcinomas, injection site sarcomas or mast cell tumors, and MCT. Additional clinical studies are necessary to define its safety in cast and efficacy.

PHARMACOLOGY/ACTIONS

Toceranib is a small molecule tyrosine kinase inhibitor (TKIs) that selectively inhibits the tyrosine kinase activity of several split kinase receptor tyrosine kinases (RTK), including VEGFR-2 (vascular endothelial growth factor receptor-2), PDGFR-Beta (platelet-derived growth factor receptor-Beta), Kit (stem cell growth factor receptor), among others. These kinases are believed to be involved in growth, pathologic angiogenesis, and metastatic processes of certain tumors. By inhibiting TKIs, toceranib competitively inhibits ATP, preventing receptor phosphorylation and subsequent downstream signal transduction. Toceranib exerts an antiproliferative effect on endothelial cells (*in vitro*) and can induce cell cycle arrest and subsequent apoptosis in tumor cell lines expressing activating mutations in Kit. As canine mast cell tumor growth can be enhanced by activating mutations in Kit, toceranib inhibition can reduce angiogenesis and subsequent growth of these cells.

Calcitriol may enhance the antiproliferative activity of toceranib in dogs with mast cell tumors and investigations exploring this potential are ongoing (Malone *et al.* 2010).

PHARMACOKINETICS

Oral bioavailability of toceranib phosphate in dogs is $\approx 77\%$. The presence of food does not significantly impact absorption. Binding to canine plasma proteins is $\approx 94\%$ and the volume of distribution is very large (>20 L/kg). Terminal elimination half-life is ≈ 17 hours (after IV) and 31 hours (oral). While the metabolic fate of toceranib has not been completely determined, it appears that the drug is metabolized via cytochrome P450 and/or flavin monooxygenase to an N-oxide metabolite. (Yancey *et al.* 2010a; Yancey *et al.* 2010b)

A study evaluating toceranib peak plasma levels after lower doses (2.5 – 2.75 mg/kg PO every other day) resulted in an average 6-8 hour post-dose plasma concentration ranging from 100-120 ng/mL. These were significantly above the 40 ng/mL concentration that is associated with target inhibition, and the adverse event profile was substantially reduced from the one associated with the labeled dose (3.25 mg/kg every other day). The authors concluded that lower dose range of toceranib should be considered for future use in dogs with cancer (Bernabe *et al.* 2013).

CONTRAINDICATIONS/PRECAUTIONS/WARNINGS

The label lists toceranib contraindications as breeding, pregnant or lactating bitches. Safe use has not been evaluated in dogs less than 24 months of age or weighing <5 kg. Because toceranib can cause vascular dysfunction leading to edema and thromboembolism (including pulmonary emboli), wait at least 3 days after stopping the drug before performing surgery.

Use caution when handling this medication. See the product's **Client Information Sheet** for more details.

- When toceranib is used in the presence of systemic mast cell tumors, significant mast cell degranulation with resultant adverse effects may result. The manufacturer states that attempts should be made to rule out systemic mastocytosis prior to starting toceranib.
- Toceranib can cause clinical signs similar to those seen with aggressive mast cell tumors, when these occur, the drug should be stopped and the patient re-evaluated (Johannes 2010). The package insert has specific monitoring requirements with dosage adjustment or therapy pause guidelines when certain adverse effects (severe diarrhea, GI bleeding) occur or when laboratory monitoring indicates toxicity. Refer to the Monitoring section below, or the package insert for more information.

ADVERSE EFFECTS

Most common adverse effects seen with toceranib in dogs include: diarrhea, decreased/loss of appetite, lameness, weight loss and blood in the stool. Severe diarrhea or GI bleeding require immediate treatment and dictate dose interruption or reduction (see monitoring below). Other

potential adverse effects include muscle cramping/pain, neutropenia, hypoalbuminemia, thromboembolic disease, vasculitis, pancreatitis, nasal depigmentation, change in coat or skin color, epistaxis, seizures and pruritus. A recent retrospective study in 20 dogs found that the majority of toceranib-treated dogs had increases in systolic blood pressure (Markovic *et al.* 2013).

One source (London 2010) suggests starting certain drugs 4-7 days prior to starting toceranib to reduce the likelihood of toxicity, including antacids (*e.g.*, famotidine, omeprazole), an antihistamine (*e.g.*, diphenhydramine), prednisone (to reduce tumor inflammation and possibly decrease mast cell tumor mediators' effects), and sucralfate (if dog has a positive stool hemoccult). Additionally, in dogs that experience inappetence or vomiting after therapy has begun, administration of metoclopramide, ondansetron, or maropitant may be effective. Loperamide can be given on toceranib dosing days to help prevent or lessen diarrhea; others have found metronidazole useful. Another author states that prednisone can be continued after treatment has begun, but should only be given on days when toceranib is not given and that NSAIDs and prednisone should never be used together (Garrett 2010).

In the small number of cats that have received toceranib, reported adverse effects include gastrointestinal toxicity, neutropenia and alopecia.

REPRODUCTIVE/NURSING SAFETY

Toceranib is a likely teratogen and should not be used in pregnant females. It is labeled as contraindicated in breeding, pregnant, or lactating bitches.

OVERDOSAGE/ACUTE TOXICITY

No acute toxicity data was located, but toceranib has a narrow margin of safety. In the event of an acute overdose, consider immediate gut decontamination; contact an animal poison center for further guidance.

DRUG INTERACTIONS

The following drug interactions have either been reported or are theoretical in humans or animals receiving toceranib and may be of significance in veterinary patients. Unless otherwise noted, use together is not necessarily contraindicated, but weigh the potential risks and perform additional monitoring when appropriate.

- **Calcitriol:** An *in vitro* study found that calcitriol had synergist effects with toceranib against canine C2 mastocytoma cells. Authors concluded that calcitriol combination therapies might have significant clinical utility in the treatment of canine mast cell tumors but refinement of the calcitriol-dosing regimen must be carried out. (Malone *et al.* 2010)
- **NSAIDs:** The package insert states to use NSAIDs with caution in conjunction with toceranib due to an increased risk of gastrointestinal ulceration or perforation. While NSAIDs (*e.g.*, piroxicam) are sometimes used with toceranib as part of metronomic drug protocols, they

should never be given on the same day as toceranib as GI toxicity can be exacerbated (London 2010).

- **CYP3A4 Inhibitors** (*e.g.*, ketoconazole, fluconazole, itraconazole, grapefruit juice, clarithromycin, verapamil): May increase toceranib concentrations. This interaction with toceranib has not been documented in dogs to date and presently is speculative, however, use caution.

LABORATORY CONSIDERATIONS

- None noted.

DOSES

Note: There is a significant amount of ongoing research evaluating toceranib for use with other drugs, other species, and for extra-label indications and since chemotherapy indications, treatment protocols, monitoring and safety guidelines often change, the following dosages should be used only as a general guide. Consultation with a veterinary oncologist and referral to current veterinary oncology references [*e.g.*, (Withrow *et al.* 2012); (Dobson *et al.* 2011); (Henry *et al.* 2009); (North *et al.* 2009); (Argyle *et al.* 2008)] are strongly recommended.

Dogs:

- **For Patnaik grade II or III, recurrent, cutaneous mast cell tumors with or without regional lymph node involvement** (labeled-dose; FDA-approved): Initial dose 3.25 mg/kg PO every other day (q48h). Dose reductions of 0.5 mg/kg (to a minimum dose of 2.2 mg/kg) every other day and dose interruptions (cessation of treatment) for up to 2 weeks may be utilized, if needed, to manage adverse reactions. May be administered with or without food. Do not split tablets. The package insert has a dosage table to determine the appropriate strength and number of tablets to use for a given dog's weight. (Adapted from label information; *Palladia*®)
- **Extra-label Doses:**
 - a. **Lower than labeled dose:** Recent clinical experience with toceranib in dogs suggests that dosing at 2.5 - 2.75 mg/kg every other day is better tolerated than the higher dose, resulting in less toxicity, better owner compliance, and fewer drug holidays. Some dogs do not tolerate this dosing regimen even at the 2.5 mg/kg dose rate. The author and some other medical oncologists have found that a M/W/F schedule of dosing may be better tolerated by some dogs. This may be particularly useful when toceranib is combined with other drugs, such as cyclophosphamide or NSAIDs as part of a metronomic treatment protocol. When a dog cannot tolerate the M/W/F schedule, every third day dosing may be attempted, but this is not ideal and may result in sub-therapeutic drug exposure. (London 2010)

- b. **In combination with piroxicam:** A small, phase-I study concluded that toceranib at labeled dosage combined with piroxicam (0.3 mg/kg PO once daily) was generally safe, but that as with the labeled dosage, GI adverse effects may occasionally require treatment holidays and toceranib dosage reduction (Chon *et al.* 2012). However, at present, it is now recommended to administer piroxicam every other day (alternating with toceranib) to avoid GI effects (London 2013).

MONITORING

- CBC, Hematocrit, Serum Albumin, Creatinine, Serum Phosphate. Manufacturer recommends weekly (approximately) veterinary assessment for the first 6 weeks of therapy and approximately every 6 weeks thereafter. The package insert states: Temporarily discontinue drug if anemia, azotemia, hypoalbuminemia, and hyperphosphatemia occur simultaneously. Resume treatment at a dose reduction of 0.5 mg/kg after 1-2 weeks when values have improved and albumin is >2.5 g/dL. Temporary treatment interruptions may be needed if any one of these occurs alone: hematocrit <26%, creatinine ≥2 mg/dL or albumin <1.5 g/dL. Then resume treatment at a dose reduction of 0.5 mg/kg once the hematocrit is >30%, the creatinine is <2.0 mg/dL, and the albumin is >2.5 g/dL. Temporarily discontinue the use of toceranib if neutrophil count is ≤1000/microL. Resume treatment after 1-2 weeks at a dose reduction of 0.5 mg/kg, when neutrophil count has returned to >1000/microL. Further dose reductions may be needed if severe neutropenia reoccurs.
- Other laboratory tests that have been suggested for monitoring early (first 6 weeks) include urinalysis and full chemistry panels.
- Adverse Effects (Diarrhea): If ≥4 watery stools/day or diarrhea persists for 2 days, stop drug and institute supportive care until formed stools recur. When dosing is resumed, decrease dose by 0.5 mg/kg.
- Adverse Effects (GI-Bleeding): If fresh blood in stool or black tarry stool for >2 days or frank hemorrhage or blood clots in stool. Stop drug and institute supportive care until resolution of all clinical signs of blood in stool, then decrease dose by 0.5 mg/kg.
- Blood pressure. (Markovic *et al.* 2013)
- Tumor Size.

CLIENT INFORMATION

- In the package insert, the manufacturer states to: "Always provide **Client Information** Sheet with prescription." In addition, it is highly recommended to verbally reiterate some of the key points found on the client information sheet, including the sections: "How do I give

Palladia™ to my dog?"; "Stop Palladia™ immediately and contact your veterinarian if you notice any of the following changes in your dog"; and "Handling Instructions".

- May be given with or without food; do not split or crush tablets.
- Toceranib is a chemotherapy (cancer) drug. The drug and its byproducts can be hazardous to other animals and people that come in contact with it. On the day your animal gets the drug and then for a few days afterward, all bodily waste (urine, feces, litter), blood, or vomit should only be handled while wearing disposable gloves. Seal the waste in a plastic bag and then place both the bag and gloves in with the regular trash.

CHEMISTRY/SYNONYMS

Toceranib phosphate is an idolinone with a molecular weight of 494.46. Toceranib may also be known as: PHA-291639, SU-11654, UNII-59L7Y0530C, toceranibum, or tocéranib.

STORAGE/STABILITY

Toceranib phosphate tablets should be stored at controlled room temperature 20-25°C (68-77°F).

COMPATIBILITY/COMPOUNDING CONSIDERATIONS

No specific information noted.

DOSAGE FORMS/REGULATORY STATUS

Veterinary-Labeled Products:

Toceranib Phosphate Oral Tablets: 10 mg, 15 mg, 50 mg; *Palladia*®; (Rx)

Human-Labeled Products: None.

REVISIONS/REFERENCES

Monograph revised/updated August 2014.

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