Sorafenib

Nexavar®

Mechanism of Action

According to the FDA NDA 021923, "sorafenib is a kinase inhibitor that decreases tumor cell proliferation in vitro. Sorafenib was shown to inhibit multiple intracellular (c-CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, RET/PTC, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis and apoptosis. Sorafenib inhibited tumor growth of HCC, RCC, and DTC human tumor xenografts in immunocompromised mice. Reductions in tumor angiogenesis were seen in models of HCC and RCC upon sorafenib treatment, and increases in tumor apoptosis were observed in models of HCC, RCC, and DTC."

Toxicology

According to the FDA NDA 021923:

In a 4-week oral gavage toxicity study, beagles were administered sorafenib at 10 (low dose), 30 (medium dose), and 60 (high dose) mg/kg. The study began with twice daily dosing (20, 60, 120 mg/kg/day); however, due to ill health (emesis, bloody diarrhea, reduced body weight gain) of the animals, dosing was reduced to once daily from day 14 onward:

- There was no NOAEL (no-observed-adverse-effect-level).
- Clinical signs: feces with bloody admixture showing reversibility during recovery period
- Mean body weight gain was reduced in treated vs. control animals.
- Clinical chemistry: included increases in AST and ALT
- Histopathological changes: observed in liver, stomach, and bone marrow next to the altered growth plate in the high dose group
- Dose-dependent alteration in the dentin composition of the teeth observed in all groups and this effect was not reversible in 28 days

In a 13-week oral gavage toxicity study, beagles were administered sorafenib at 10 (low dose), 30 (medium dose), and 60 (high dose) mg/kg/day:

- One female beagle given 10 mg/kg was sacrificed moribund at the end of week 13 of the study with findings correlating with a marked to severe purulent pleuropnuemonia and a moderate chronic adhesive pericarditis.
- In surviving animals, the nutritional state, food consumption, and body weight gain were reduced at doses ≥ 30 mg/kg/day (AST, ALT, ALP, GGT).
- Histopathology: the liver showed minimal to moderate bile duct proliferation and minimal to slight periportal fibrosis. Other changes were seen in the kidneys (increased number of basophilic tubules, proteinaceous casts, glomerulopathy, increased PAS positive reaction of

tubules and/or glomerula), the lymphoreticular/hematopoietic system (atrophy of thymus and spleen, increased hematopoiesis and perifollicular granulocytic infiltration in the spleen, necrosis of lymphoid follicles in the tonsils, atrophy of lymphoid follicles of the ileum, increased number of granulocytes in the sternum and in the bone marrow cylinders), teeth (altered dentin composition), large intestine (increased number of goblet cells), and skin (alopecia/degeneration of hair follicles).

In a 52-week (1-year) oral gavage toxicity study, beagles were administered sorafenib at 3 (low dose, LD), 10 (low medium dose, LMD), 30 (high medium dose, HMD), and 60 (high dose, HD) mg/kg/day.

- There were 6 unscheduled deaths: 1 in control group (from inhalation pneumonia likely due to gavage), and 5 in the HMD and HD groups which appeared to be due to purulent myocarditis, nephritis, adn pyemia, which were most probably caused by alopecia with peri/folliculitis.
- Decreased body weight gain starting with LD
- Clinical signs:
    - Skin/hair: sparse hair coat, slight hair loss, and pustules with LMD, alopecia with reddedn or bluish skin areas with HMD, and dark axillary skin in HD group
    - Feces: liquid feces starting at LMD, yellow and red colored mucus excreted at HMD and HD
    - Conjunctivitis with mucous coating starting at LMD.
- Hematology: mainly at HD, increased leukocytes, neutrophils, and monocytes. Increased Heinz bodies, decreased erythrocytes/hemoglobin/hematocrit with increased splenic iron deposition. Increased platelets.
- Clinical chemistry: increased ALT, AST, ALP, GGT. Hypothyroidism (decreased T3, T4, adn increased TSH)
- Urinalysis: no relevant changes
- Histopathology: kidneys (glomerulopathy tubular dilation, reduced pigment deposition), spleen (increased iron deposition), bone marrow (hypocellularity and increased fat), femoral bone (incomplete epiphyseal closing), male reproductive system (tubular degeneration and dilation, oligospermia), adrenal glands (single cell necrosis), teeth (dentin alteration), lymphatic tissues (depletion, atrophy, necrosis), GI tract (inflammation, hemorrhage, glandular dilation), liver (cirrhosis, bile duct proliferation)

FDA Labeled Use

Nexavar® is not labeled for dogs; therefore, use of this drug in the dog is off-label.

According to the FDA's Highlights of Prescribing Information (Reference ID 4641404):

Nexavar® is a kinase inhibitor indicated for the treatment of

- Unresectable hepatocellular carcinoma
- Advanced renal cell carcinoma

- Locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment

Selected Canine Publications

Preclinical

- In an *in vitro* study, A significant decrease of neoplastic cells was observed in D-17 osteosarcoma cell lines after incubation with 0.5 - 16 uM sorafenib. There were significantly more cells immunocytochemically positive for caspase 3 (indicative of apoptosis), and paradoxically higher expression of Ki-67 (nuclear proliferation marker) in sorafenib treated cells (Wolfesberger et al.).
- In an *in vitro* study, hemangiosarcoma-derived primary cells were sensitive to sorafenib. *In vivo*, sorafenib decreased tumor size in both cutaneous cell-derived xenografts and cardiac tumorgrafts (Anderson NJ et al.).
- Two canine mammary gland tumor primary cell lines were susceptible to sorafenib,with an IC_{50} of 1.34 µM and 2.61 µM (Prado MC et al.).
- Five canine TCC cell lines in which BRAFV595E mutation was observed (Sora, Love, MCTCC, LCTCC, and TCCUB) were found to express VEGFR-2 and PDGFR-ß. Cell cycle arrest at the G0/G1 phase, subsequent apoptosis, and growth inhibition were observed following sorafenib treatment. Sorafenib (30 mg/kg/day) inhibited tumor growth and inhibited angiogenesis in the tumor microenvironment in nude mice injected with the Sora cell line subcutaneously (Yokota et al.).
- Novel canine TCC cell lines were established form 2 tumor tissues and one metastatic lymph node of canine TCC patients harboring the BRAF V595E mutation. Tumor tissues highly expressed the BRAF mutant and phosphorylated extracellular signal-related kinases (ERK)½ proteins. The derived cell lines demonstrated activated MAPK pathways, and sorafenib successfully inhibited the BRAF/MAPK pathway and induced apoptosis. The established cell lines responded with greater sensitivity to sorafenib than to vemurafenib (Jung et al.).

Safety/dosing and Efficacy

- In a prospective non-randomized, non-blinded, single center clinical trial of dogs with advanced, unresectable hepatocellular carcinoma, 7 dogs given sorafenib (@ 5 mg/kg twice daily) had a significantly longer median time to progression of 363 days and median overall survival of 361 days compared to 6 dogs treated with metronomic thalidomide, piroxicam, and cyclophosphamide. Side effects with sorafenib included cutaneous toxicity (grade 2 alopecia, grade 1 hyperpigmentation, grade 1 localized erythema and alopecia) and diarrhea (grade 1). Hyperbilirubinemia and serum transaminase elevations did not occur (Marconato L et al.).
- In an early phase tolerability study of sorafenib in client-owner dogs with a diagnosis of cancer, a once-weekly dose at 3 mg/kg was tolerable. One dog with an oral malignant

melanoma had a measurable tumor response. In 3 dogs, all with bladder TCC, no disease progression was noted for greater than 4 weeks (Foskett A et al.).

- A positive response was noted for a dog with a BRAF V595E mutation with elevated VEGFR-1 expression in a urothelial TCC with metastasis to the sublumbar lymph nodes, with the tumor surgically debulked with gross residual tumor and lymph nodes removed *in toto*; mitoxantrone administered but discontinued with dose-limiting side effects; piroxicam and sorafenib started at 4 mg/kg/day and increased to 10 mg/kg/day over 6 weeks, and dysuria disappearing 4 weeks after the sorafenib dose was increased to 10 mg/kg in combination with piroxicam (Kim JH et al.).

Pharmacokinetics

According to the FDA NDA 021923:

- Based on SINGLE-DOSE PK studies:
  - Plasma clearance 0.13-0.15 L/h/kg.
  - Vss moderate, approximately 0.7 L/kg.
  - Plasma elimination $t_{1/2}$ of unchanged substance was 4 hours in dogs, independent from route of administration.
- Based on REPEAT-DOSE PK studies:
  - Reduced absorption was observed at higher doses in the toxicology studies, attributed to the poor solubility of the test article at higher doses.
  - There was potential for drug accumulation after repeated dosing for the low and intermediate doses.
  - There appeared to be potential for metabolic auto-induction of sorafenib metabolism at high doses.
- Protein binding was high. The fraction unbound to plasma proteins (fu) was 0.9%.
- Absorption was only 68% when compound was given as a single oral dose equivalent to 82 mg/m^2 of the free base.
- Excretion was mainly via the biliary/fecal route (90% excretion); urinary excretion was low (<1%).
- Plasma elimination half life of unchanged compound was 4 hours.

Doses of BAY 43-9006	10 (mg/kg)		30 (mg/kg)		60 (mg/kg)	
Week 4	Females	Males	Females	Males	Females	Males
AUC $_{(0\text{-}24)}$ (mg*h/l)	19.01	15.33	45.16	34.37	66.2	40.71
Cmax	2.04	2.29	5	3.17	5.67	4.94

- $AUC_{(0\text{-}24)}$ 15326 - 19007 µg*h/L, C_{max} 2043-2292 µg/L @ 10 mg/kg BID for first 14 days, then q24 hours onward. Females exhibited higher exposure levels compared to males which appeared to increase with dose (increase 20% at 10 mg/kg, increase 60% at 60 mg/kg). However, in the 1-year toxicology study at 3, 10, 30, and 60 mg/kg study

(toxicokinetics measured on weeks 1 and 18), there was no significant gender related differences in plasma concentrations.

Dose (mg/kg)	Day 1 0 h	1 h	3 h	7 h	24 h	AUC 0-24 (ug*h/l)	AUC 0-24,n (g*h/l)	Cmax (ug/l)	Cmax,n (g/l)	tmax* (h)
3	<LOQ	180.1	297.0	151.1	33.8	2953.9	984.6	304.9	101.6	5.4
10	<LOQ	564.9	661.5	363.8	149.7	7882.3	788.2	737.0	73.7	2.3
30	<LOQ	1678.5	1897.1	1162.6	506.5	26589.1	886.3	2116.1	70.5	7.8
60	<LOQ	3248.5	2928.0	1911.8	1164.2	47008.0	783.5	3381.4	56.4	4.9
	Week 18 0 h	1 h	3 h	7 h	24 h	AUC 0-24 (ug*h/l)	AUC 0-24,n (g*h/l)	Cmax (ug/l)	Cmax,n (g/l)	tmax* (h)
3	65.6	218.9	392.5	277.3	38.3	4286.2	1428.7	408.9	136.3	2.8
10	263.4	819.6	1342.9	882.8	187.2	15128.3	1512.8	1358.3	135.8	3.5
30	234.6	1420.4	2624.2	1750.1	663.1	36300.7	1210.0	3044.3	101.5	3.8
60	506.9	3289.5	3590.6	2213.7	320.3	37632.0	627.2	3757.4	62.6	2.0

Sources

- Best Pet Rx+ (https://bestpetrx.com/): (as of August 7, 2021) Available in dose range 0.1 mg - 125 mg capsules

Dose 0.1 mg capsules, quantity 30, $165.50.
Dose 125 mg capsules, quantity 30, $258.99.

+Please check their website to confirm that they can serve your state.

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of August 31, 2021) Available in dose range 25 mg to 150 mg capsules

Dose 25 mg capsules, quantity 30, $450.
Dose 150 mg capsules, quantity 30, $600.

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/veterinary-practices/): (as of September 29, 2021) Available in capsule dose range* 10 mg - 196 mg and oral oil suspensions*

10 mg capsules, quantity 30, $76.
196 mg capsules, quantity 30, $1,080.

Oral oil suspensions, 2 concentrations*

Concentration 14 mg/mL, 10 mL bottle, $72
Concentration 45.6 mg/mL, 25 mL bottle, $129.75

**This dose range/concentrations may not appear on your online portal. If so, please call Wedgewood Pharmacy (call center 877.357.6613) to prescribe this drug.*

Anecdotal Information from Veterinary Oncologists

None currently

References

Anderson NJ et al. Pharmacologic inhibition of MEK signaling prevents growth of canine hemangiosarcoma. *Mol Cancer Ther*. 2013 Sep;12(9):1701-14. doi:10.1158/1535-7163.MCT-12-0893

Foskett A et al. Tolerability of oral sorafenib in pet dogs with a diagnosis of cancer. *Vet Med (Auckl)*. 2017 Dec 8;8:97-102. doi: 10.2147/VMRR.S149678.

Jung H et al. Establishment of canine transitional cell carcinoma cell lines harboring BRAF V595E mutation as a therapeutic target. *Int J Mol Sci*. 2021 Aug 25;22(17):9151. doi: 0.3390/ijms22179151.

Kim JH et al. Longitudinal assessment of B-RAF V595E levels in the peripheral cell-free tumor DNA of a 10-year-old spayed female Korean Jindo dog with unresectable metastatic urethral transitional cell carcinoma for monitoring the treatment response to a RAF inhibitor (sorafenib). *Vet Q*. 2021 Dec;41(1):153-162. doi: 10.1080/01652176.2021.1905194.

Marconato L et al. Sorafenib for the treatment of unresectable hepatocellular carcinoma: preliminary toxicity and activity data in dogs. *Cancers (Basel)*. 2020 May 18;12(5):1272. doi:10.3390/cancers12051272.

Nexavar® (Sorafenib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 021923, December 2005.

Prado MC et al. Investigation of the prognostic significance of vasculogenic mimicry and its inhibition by sorafenib in canine mammary gland tumors. *Front Oncol*. 2019 Dec 19;9:1445. doi: 10.3389/fonc.2019.01445

Wolfesberger B et al. The tyrosine kinase inhibitor sorafenib decreases cell number and induces apoptosis in a canine osteosarcoma cell line. *Res Vet Sci*. 2010 Feb;88(1):94-100. doi:10.1016/j.rvsc.2009.06.009

Yokota S et al. Sorafenib inhibits tumor cell growth and angiogenesis in canine transitional cell carcinoma. *J Vet Med Sci*. 2022 Apr 5. doi: 10.1292/jvms.21-0478.

treating veterinarian is encouraged to refer to drug labeling, published literature, and safety data for warnings, precautions, and dosing guidelines. Referenced articles, if any, were manually selected and do not necessarily reflect the entirety of literature on the drug or drugs. Vidium Animal Health®'s services, including but not limited to the information contained herein, are governed by Vidium's Terms & Conditions, which are available via email by requesting them at vidiuminfo@tgen.org.

Questions? Call Vidium Customer Support at (833) 794-0318, email VidiumInfo@tgen.org, or visit www.vidiumah.com

v 26APR2022