Dasatinib

Sprycel®

Mechanism of Action

According to the FDA NDA 021986, "dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase.

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib was able to overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression."

Toxicology

According to the European Medicines Agency, "an exploratory repeat-dose toxicity study conducted in two dogs was discontinued after two days due to gastrointestinal toxicity (930003268). Dasatinib treatment (5 mg/kg) induced emesis and bloody vomitus and liquid, mucous and bloody faeces within 2 hours post-dosing. Additional findings consisted of red discoloration of the mesenteric lymph node and mucosae of the stomach, small intestine and colon. Microscopically, thymic lymphoid depletion was observed in the female. Decreases in total protein, albumin, and globulins were observed."

FDA Labeled Use

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

According to the FDA's Highlights of Prescribing Information (Reference ID 4818663), Sprycel® is a kinase inhibitor indicated for the treatment of

- newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.
- pediatric patients 1 year of age and older with Ph+ CML in chronic phase.
- pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy.

Selected Canine Publications

:: Preclinical

- In an *in vitro* study, dasatinib suppressed osteosarcoma cell viability and hepatocyte growth factor (HGF)-induced invasion and migration (Marley et al.).
- In a cell line established from an appendicular osteosarcoma, tumor cell sensitivity to a panel of small molecule inhibitors showed an IC_{50} of 151 nM for dasatinib. Serum levels obtained while the patient was on a stable dose of 0.75 mg/kg/day demonstrated that a concentration known to be therapeutic in humans (30 nM) was achieved by 1-hour post-dose and maintained for more than 4 hours (with $AUC_{0\text{-}6h}$ = 99.6ng*hr/mL). Plasma levels of dasatinib were undetectable at 0.5 mg/kg/day (Davis et al.).
- In an *in vitro* study, dasatinib was a potent inhibitor of hemangiosarcoma cell viability, inhibited PDGFR-β and Src Phosphorylation in canine hemangiosarcoma cells, and potentiated doxorubicin cytotoxicity (Dickerson et al.).
- The IC_{50}s of dasatinib were 10 and 9 nM for histiocytic sarcoma (HS) cell lines BD and DH82, respectively, and and the combination of dasatinib and doxorubicin synergistically increased the inhibitory effect on the growth of DH82 cells (although not BD cells, Takada et al, 2018). Dasatinib treatment of mice with intrasplenic xenografts (BD cell line) decreased tumor growth and increased survival times (Takada et al., 2019). Dasatinib was also shown to inhibit the growth of 4 other HS cell lines (CHS-1, CHS-2, CHS-4, CHS-7) with IC_{50} values of 5.4 - 54.5 nM (Ito et al.).
- Dasatinib caused dose-dependent inhibition of proliferation in C2 mast cells, with an IC_{50} of 12 +/- 3 nM, and growth inhibitory effects were associated with cell-cycle arrest and apoptosis (Gleixner et al.).
- Dasatinib decreased migration and metastasis in the $HER2^{+}$ and $PTEN^{-}$ CMT-U27 canine mammary cell line (Timmermans-Sprang et al.).

:: Safety/dosing

- A Golden Retriever with appendicular osteosarcoma had lethargy grade 2, GI toxicity grade 1, and neutropenia grade 1 with dasatinib 1 mg/kg/day. The dose was reduced to 0.75 mg/kg/day (considered this dog's maximum tolerated dose), which was well-tolerated and maintained for 14 weeks. An accidental overdose (single dose at 1.5 mg/kg) resulted in elevated ALT and single episode of hematochezia (Davis et al.).
- An 11-yr-old Golden Retriever with hemangiosarcoma affecting the heart, liver, spleen, and lungs received cardiac surgery to debulk the tumor, after which dasatinib was administered orally and gradually escalated to 1 mg/kg given on 2-4 consecutive days followed by a rest day. Doxorubicin was administered concurrently. Antinausea prophylaxis was provided, and the dog tolerated this regimen well with occasional periods of reduced appetite that were transient. There were no abnormalities detected on routine blood counts and serum biochemical screens. After 3 months, abdominal hemorrhage secondary to bleeding from hepatic hemangiosarcoma metastases required surgical intervention, and the dog succumbed to postoperative complications (Dickerson et al.).

- In 4 male Beagles with median weight 8.59 kg who received pre-treatment with famotidine (40 mg/dog) 3 hours prior to receiving one 50 mg tablet of dasatinib, measurable plasma concentrations of dasatinib decreased 30-fold. Famotidine increased the gastric pH from 2.62 to 7.08 and 7.3 at 1 and 2 h post-famotidine treatment, respectively (Pang et al.).

:: Efficacy

- Three large breed dogs with proximal tibial osteosarcoma had limb amputation and 5 cycles of carboplatin chemotherapy every 3 weeks (@300 mg/m2), and dasatinib treatment commenced 3 weeks after the completion of carboplatin chemotherapy, at which time all dogs were free of radiographically detectable pulmonary metastases. Another 1 dog commenced dasatinib when pulmonary metastases were detected after 3 of 5 planned carboplatin treatments. A single, 1 cm pulmonary nodule appeared to resolve after 3 months of dasatinib treatments, and this dog continued on dasatinib for a total of 25 months (did not receive any additional carboplatin chemotherapy. The starting dose of dasatinib in all dogs was 0.5 mg/kg, given everyday or every other day. The primary adverse events were inappetence and gastrointestinal upset with diarrhea. After 2 weeks without significant adverse effects, the 0.5 mg/kg dose was increased to 0.75 mg/kg and continued indefinitely or until the owner's decision to stop. Doses higher than 0.75 mg/kg were generally not tolerated. Patient characteristics and survival time are tabulated below (Table 1, excerpted from Marley et al.).

Table 1. Patient Characteristics, Survival and Treatments

Dog Signalment	Tumor Location	Survival Time	Dasatinib Treatment
Golden Retriever 7 y old, MN	Left proximal tibia	29 mo*	0.5-0.75 mg/kg Q24 6.5 mo
Labrador Retriever 4 y old, MN	Left proximal tibia	28 mo*	0.5-0.75 mg/kg EOD 10 mo
German Shepherd mix 9 y old, MN	Right proximal tibia	33 mo; still living	0.5-0.75 mg/kg Q24 25 mo
Great Pyrenees 10 y old, MN	Right proximal tibia	15 mo*	0.5-0.75 mg/kg EOD 7 mo

Q24, every 24 hours; *EOD*, every other day; *MN*, male neutered.
* Death due to metastatic disease.

Pharmacokinetics

- Unbound fraction in plasma 0.042 (Hoshino-Yoshino et al.).
- AUC_{last} 0.7 μM*h, C_{max} 0.09 μM), T_{max} 9.8 h (in dogs received mean 5.8 mg/kg since oral tablet dose, Pang et al.).
- For 3 beagles after having received 3 mg/kg PO dasatinib: (excerpted from Kamath et al.):

Parameter	Dog (n = 3)	
	IV	Oral
Dose (mg/kg)	1.2	3
C_{max} (μM)	–	0.30 ± 0.09
T_{max} (h)	–	0.75 ± 0.25
AUC_{tot} (μM × h)	1.67 ± 0.41	1.4 ± 0.36
CL (ml/min/kg)	25 ± 6.3	–
V_{ss} (l/kg)	4.7 ± 0.8	–
$t_{1/2}$ (h)	4.2 ± 2.0	5.0 ± 1.8
MRT (h)	3.2 ± 0.8	5.8 ± 1.1
Bioavailability (%)	–	34 ± 13
Percentage of dose excreted in urine as parent (0–24 h)	0.7 ± 0.3	0.8

Sources

- Best Pet Rx+ (https://bestpetrx.com/contact-us/): (as of September 7, 2021) Available in dose range of 0.1 mg - 25 mg capsules:

Dose 0.1 mg, quantity 30: $126.50

Dose 25 mg, quantity 30: $146.50

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

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of September 29, 2021) Unavailable.

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/veterinary-practices/): (as of September 29, 2021) Available in dose range* of 0.5 mg - 45 mg capsules

Dose 0.5 mg, quantity 30: $68.50

Dose 45 mg, quantity 30: $137.50

**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

"Starting dose is 0.33 mg/kg for 2 weeks, then doubled to 0.66 mg/kg/day for 2 weeks. If they are doing well, then try 1 mg/kg/day."

"Causes GI upset, anorexia, and diarrhea; if noted, back down to the last tolerated dose or try every other day dosing. Side effects pass quickly once the drug is stopped.

References

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Timmermans-Sprang et al. Dasatinib inhibition of cSRC prevents the migration and metastasis of canine mammary cancer cells with enhanced Ent and HER signalling. *Vet Comp Oncol*. 2019 Sep;17(3):413-426. doi: 10.1111/vco.12490.

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