Ibrutinib

Imbruvica®

Mechanism of Action

According to the FDA NDA 205552, "ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion *in vitro*."

Toxicology

According to the NDA 205552, dogs tolerated oral doses of ibrutinib up to 200 mg/kg, with mild ataxia and/or hypoactivity at 2 hours post-dosing.

Multi-dose study: In dogs given ibrutinib at 1.5 (LD), 24 (MD), or 150 (HD) mg/kg/day via oral gavage for 28 days,

- Major findings included **GI toxicities** (inflammation/atrophy, diarrhea/mucoid feces), and unresolved corneal dystrophy at **HD**.
- Food consumption decreased by 16-20% in the MD and HD groups during weeks 1-2.
- EKGs were unremarkable at all doses (2 hours post-dose on days 2 and 22) (although when given at single doses, there was a dose-dependent RR interval prolongation and decreased heart rate).
- Hematology changes (noted on day 25) included **leukocytosis** by 13-36% for LD, MD, HD groups; **thrombocytosis** by 19-24% in the HD group; **neutrophilia** in the HD group
- Clinical chemistry changes included **increase in ALP** by 13% in the HD group (on day 57); **increase in AST** by 41-55% in the LD and HD groups (on day 25), and **increase in triglycerides** by 30-53% in the HD group (on days 25-57).
- Histopathology findings included **mild chronic inflammation** in the cecum, colon, ilium, and rectum, only in the HD group.

Multi-dose study: In dogs given ibrutinib at 30, 80 (later 60), or 220 (later 120) mg/kg/day via oral gavage for 13 weeks:

- Doses were lowered from 80 to 60 and 220 to 120 mg/kg/day due to 2 drug-related moribund sacrifices on day 31. The cause of morbidity was determined to be **treatment-related enterocolitis** (given 220 mg/kg/day) and **severe acute lung inflammation and bacterial colonization in the lungs** (given 80 mg/kg/day). Clinical signs in the 2 moribund sacrificed dogs included hypoactivity, dermal atonia, red nasal discharge, diarrhea, swollen facial area, and raised reddened areas on the gums.
- Drug-related clinical signs of toxicity were primarily noted in the 80/60 and 220/120 mg/kg/day groups. Clinical signs included **abnormal excreta** (soft feces and/or diarrhea),

emesis, reddened or pale gums, raised reddened or white areas on the gums. Signs suggestive of **effects on the CNS** included continuous tremors, intermittent convulsion and rigid muscle tone, and were generally resolved during the recovery period. Dogs in the 220/120 mg/kg/day group showed reduction of weight gain compared to control dogs.

- There were slight perturbations in erythroid parameters (lower RBC, HGB, HCT, increased RDW and HDW), slight thrombocytosis, and increased aPTT in the 220/120 mg/kg/day group.
- Drug-related decreases in serum albumin and GGT were noted at 80/60 and 220/120 mg/kg/day doses; findings were reversible.
- There were no drug-related urinalysis findings.
- Pathology findings included drug-related red areas in the cecum and ileum, correlating with acute inflammation microscopically. Microscopic findings were absent at the end of the recovery phase.

FDA Labeled Use

Ibrutinib 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 5176202), Imbruvica® is a kinase inhibitor indicated for the treatment of

- Adult patients with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).
- Adult patients with chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion.
- Adult patients with Waldenström's macroglobulinemia (WM).
- Adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

Selected Canine Publications

:: Preclinical

- In a cell-line study, ibrutinib showed anti-proliferative effects on a canine DLBCL cell line (CLBL-1), a canine B-cell leukemia cell line (GL-1), and in a human DLBCL cell line (SU-DHL-4, Kong et al.).
- In an evaluation of ibrutinib's effects on 2 canine mast cell lines (C2 and NI-1) and on primary mast cells obtained from canine mast cell tumors, ibrutinib exerted anti-proliferative effects and counteracted IgE-dependent histamine release in these cells. Ibrutinib suppressed phosphorylation of BTK and of downstream STAT5 in both mast cell lines. At higher concentrations, ibrutinib also induced apoptosis in both mast cell lines (Gamperl et al.).

:: Safety/dosing

- Please see study (Honigberg et al.) in Efficacy section below.

:: Efficacy

- In 8 dogs with naturally occurring, treatment-naive or relapsed B-cell lymphoma receiving ibrutinib in doses ranging from 2.5 to 20 mg/kg/day, there were 3 partial responses, 3 with stable disease, and 2 with progressive disease (see table below). Inhibition of Btk was monitored *in vivo* by labeling PBMCs and tumor lysates. In 5 dogs in which tissue samples were analyzed, a single administration of ibrutinib at dosage levels ranging from 2.5 - 20 mg/kg/day was sufficient to fully occupy Btk in peripheral blood and tumor tissue for 24 hours (Honigberg et al.).

Adapted from Honigberg et al.

Dog	Stage	Histology	PARR (monoclonal BCR)	Previous Treatment	Dose, mg/kg	Outcome (RECIST)	Progression free interval, d	Decrease in tumor sums, %
A1	IIIa	NA	—	—	20	SD	28	10
A2	Va	NA	+	COP	20	PD	0	—
A3	IIIa	Follicular large cell	—	CHOP	20	SD	14	—
A4	IIIa	Diffuse immunoblastic	+	COP	20	PR	35	77
B1	IIIa	Diffuse immunoblastic	+	—	2.5/5.0/7.5	SD	21	—
B2	IIIa	Follicular large cell	+	—	2.5/5.0	PR	70	31
B3	IIIa	Diffuse immunoblastic	+	—	2.5	PD	0	—
B4	Va	Follicular large cell	+	—	2.5/5.0	PR	63	62

CR, complete response; NA, not applicable; PARR, PCR of antigen receptor rearrangement; PD, progressive disease; PR, partial response; SD, stable disease.

Pharmacokinetics

According to the NDA 205552,

- Oral bioavailability of ibrutinib was low at 7-11%.
- Orally administered ibrutinib was absorbed fairly rapidly (T_{max} 0.5 - 4 hours) and was highly bound to plasma proteins (96-99%).
- According to the table below (Table 19), on day 24, the T_{max} values increased in a dose related manner from 1 - 10 hours for males, compared to 1 - 3.4 hours for females.

Table 19- Toxicokinetic parameters: 4-week study in dogs

Parameter/	Males (mg/kg)			Females (mg/kg)		
Day 1	1.5	24	150	1.5	24	150
AUC last (ug.h/mL)	0.0053	1.78	2.02	0.0097	1.00	4.72
Normalized AUC	0.0035	0.074	0.014	0.0064	0.083	0.032
Cmax (ug/mL)	0.0035	0.95	0.75	0.0056	0.86	1.71
Normalized Cmax	0.0023	0.04	0.005	0.0037	0.036	0.011
t1/2 (h)	0.82	3.1	4.2	1.1	2.4	4.0
Day 24						
AUC last (ug.h/mL)	0.017	1.54	14.1	0.021	1.85	15.2
Normalized AUC	0.012	0.064	0.094	0.014	0.08	0.10
Cmax (ug/mL)	0.01	0.68	1.48	0.01	0.91	2.18
Normalized Cmax	0.007	0.03	0.01	0.007	0.038	0.015
t1/2 (h)	1	2.5	2.3	2.7	2.5	2.4

Sources

- Best Pet Rx[+] (https://bestpetrx.com/contact-us/): (as of May 15, 2023) Available.
  Dose 25 mg capsules, quantity 30, ~$164.50.
  Dose 50 mg capsules, quantity 30, ~$221.50.
  [+]Please check their website to confirm that they can serve your state.

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of May 2023) Unavailable.

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/):
(as of June 2023) Available.
  Dose 4 mg capsules, quantity 30, ~$69
  Dose 90 mg capsules, quantity 30, ~$198.
**This dose range 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

Common starting doses are 2.5 - 5 mg/kg/day.

References

Gamperl et al. Effects of ibrutinib on proliferation and histamine release in canine neoplastic mast cells. *Vet Comp Oncol*. 2019 Dec;17(4):553-561.

Honigberg et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci U S A.* 2010 Jul 20;107(29):13075-80. doi: 10.1073/pnas.1004594107.

Imbruvica® (Ibrutinib); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 205552 (capsule), February 2014.

Jiang et al. Simultaneous measurement of acalabrutinib, ibrutinib, and their metabolites in beagle dog plasma by UPLC-MS/MS and its application to a pharmacokinetic study. *J Pharm Biomed Anal.* 2020 Nov 30;191:113613. doi: 10.1016/j.jpba.2020.113613.

Kong et al. BTK and PI3K inhibitors reveal synergistic inhibitory anti-tumoral effects in canine diffuse large B-cell lymphoma cells. *Int J Mol Sci*. 2021 Nov 24;22(23):12673. doi: 10.3390/ijms222312673.

drug costs and availability are subject to change at the discretion of the providing pharmacy. The 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 05JUN2023