Vorinostat

Zolinza®

Mechanism of Action

According to the FDA's Highlights of Prescribing Information (Reference ID 4361149): Vorinostat inhibits the enzymatic activity of histone deacetylases HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II) at nanomolar concentrations (IC50<86 nM). These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. In some cancer cells, there is an overexpression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation. *In vitro*, vorinostat causes the accumulation of acetylated histones and induces cell cycle arrest and/or apoptosis of some transformed cells. The mechanism of the antineoplastic effect of vorinostat has not been fully characterized.

Toxicology

According to the FDA NDA 21991:

SINGLE dose:

- 4-hour **IV infusion** at 48, 68, 96, 150, and 200 mg/kg to Beagle dogs:
  - 48 mg/kg: no clinical signs. NOAEL
  - 68 mg/kg, Day 3: *decreased* WBC by 27%, neutrophils by 24%, monocytes by 73%, and eosinophils by 45%.
  - 96 mg/kg, Day 3: *decreased* WBC by 33%, neutrophils by 27%, monocytes by 100%. Reversible Day 7.
  - 150 mg/kg: emesis and increased bilirubin; decreased body weight, increased WBC, neutrophils and ALT in male; decreased WBC and neutrophils in female
  - 200 mg/kg: emesis, biting, aggression, salivation, vocalization, decreased body weight. Day 3: increased ALT and Bili; decreased WBC, neutrophil, Hg in female; increased WBC and neutrophil and decreased Hg in male
- 120-hour **IV infusion** at 72 and 144 mg/kg/day to Beagle dogs:
  - 72 mg/kg/day: ataxia, muscle rigidity, recumbent at 52 hours with tremors and rapid respiration. Decreased K, Cl, WBC, Lymph, Mono/eso, Retic, Neutro (seg); increased ALP/AST/ALT, CPK, BUN, LDH, Chol, PTT. Moribund and euthanized at 72 hours.
  - 144 mg/kg/day: Similar findings as above, as early as 48 hours.

MULTIPLE doses:

- In a **4-week** repeat dose, **oral gavage** toxicology study with a 2-week recovery in Beagle dogs, treated with 0, 15, 40, or 100 mg/kg/day daily for 28 days:

- **Clinical signs** [thin appearance, dehydration, hypoactive behavior, abnormal fecal excretion (discolored, liquid, mucoid, non-formed), pale gums, and emesis] **resulted in the sacrifice** of 3 dogs/sex in the **high dose group (HD, 100 mg/kg/day)** on Day 17. In the remainder of high-dose dogs, the dogs were designated for recovery and sacrificed days 29/30. Mortality was not observed below 100 mg/kg. Clinical signs in the low and mid dose groups were similar but lower in magnitude.
- **20% body weight decrease in HD group; full recovery not observed**.
- No treatment-related findings in ophthalmology, electrocardiology, or indirect BP.
- Clinical pathology findings in HD group, evaluated on Day 17: increased or decreased hemoglobin and hematocrit; increased WBC, neutrophils, monocytes; decreased lymphocytes; increased APTT, total protein, albumin, serum creatinine, BUN; decreased electrolytes (P, Na, K, Cl); increased BG, platelets; increased urine volume and decreased USG, and positive occult blood in urine.
- At recovery, all values normalized except hemoglobin, erythrocyte counts, and HCT
- No macroscopic findings on days 29 and 30.
- Microscopic findings included gastroenteropathy, increased splenic pigment, hypocellular bone marrow, testicular degeneration at HD at Day 17, and persisted to Day 29. **No treatment-related changes in 15 or 40 mg/kg/day dose groups.**

- In a 26-week, repeat-dose oral (capsules) toxicity study with a 4-week recovery in Beagle dogs, **no adverse events** were found at doses of **20 mg/kg/day (400 mg/m2/day) or 60 mg/kd/day (1200 mg/m2/day).** Due to lack of findings, doses began at 80 mg/kg/day and escalated in succession to 100, 125, and 160 mg/kg/day on drug days 16, 30, 97, respectively.
  - At **160 mg/kg/day,** there was **reversible GI toxicity**, characterized by non-formed or liquid feces, macroscopic (red foci) or microscopic (villous blunting with crypt epithelium regeneration, inflammation and necrosis in the large and small intestines) findings. Additional changes to the study protocol included **additional time to the feeding window (at least 12 hours) which appears to have abrogated dose limiting GI toxicity.**
  - Histologically, there was **no evidence of serious, irreversible damage to any organ**. No treatment-related findings at any dose were noted for mean body weight, food consumption, ophthalmologic and electrocardiographic parameters, or blood pressure.
  - Based on this study, the no-observable-adverse-effect level (**NOAEL**) was **60 mg/kg/day** (1200 mg/m2/day).

FDA Labeled Use

Zolinza® 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 4361149), Zolinza® is a histone deacetylase (HDAC) inhibitor indicated for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.

Selected Canine Publications

:: Preclinical

- In a preclinical study, 13 FDA-approved drugs were identified after screening of an FDA-approved drug library (Parrales et al.). Auranofin (an oral drug used for the treatment of rheumatoid arthritis in people) was selected for demonstrating high cytotoxicity. Combination of auranofin with **vorinostat** or rapamycin cooperatively induced apoptosis in osteosarcoma cell lines; the combinations (IP injections, vorinostat dose at 2.5 mg/kg) also significantly suppressed tumor growth in tumor-bearing nude mice and were well tolerated.

- In a study of 9 canine cancer cell lines (Kisseberth et al.) treated with 2 HDAC inhibitors (OSU-HDAC42 and SAHA), concentrations of SAHA required to achieve IC_{50} were reached in cells of 4 canine cancer cell lines and ranged from 0.6 to 4.8 µM. Cells from T-cell lymphoma, mast cell tumor, osteosarcoma, and histiocytic sarcoma lines were most sensitive to HDAC inhibition, with IC_{50} < 5 µM for SAHA.

- In an osteosarcoma cell line study (Murahari et al.), SAHA reduced the viability of canine and human osteosarcoma cells in a dose-dependent manner, induced dose-dependent apoptosis, and inhibited HDAC activity.

- In a preclinical study, vorinostat inhibited the growth of 6 canine urothelial carcinoma cell lines in a dose-dependent manner and induced G0/G1 cell cycle arrest. ; mediated the acetylation of histone H3, the dephosphorylation of p-Rb, and the upregulation of p21 upon exposure to vorinostat; and inhibition of tumor growth was observed in xenografted mice (Eto et al.)

- On an in vitro study evaluating the effect of SAHA on the cytotoxicity of IL-2 activated PBMC in 3 tumor cell lines (CTAC [from canine thyroid carcinoma], CIPm [metastatic canine tubular adenocarcinoma], MCM-N1 [canine malignant oral melanoma]), SAHA sensitized the canine tumor cells to cytotoxicity due to PBMC activation and also suppressed the cytotoxicity of PBMC themselves (Oyamada et al).

- In a hemangiosarcoma cell line study, SAHA induced apoptosis and upregulated inflammatory-related genes and attracted macrophages, suggesting that SAHA can affect immune responses. SAHA did not affect tumour growth (Suzuki et al.).

:: Safety/dosing

- A 26-week, repeat-dose oral (capsules) toxicity study with a 4-week recovery in Beagle dogs performed and reported in the NDA above was also published (Kerr et al.). Age ranged from 7-12 months, and group sizes were 3-6/sex/group. There were several other take-aways in addition to the main findings listed above:
    - In a prior oral exploratory repeated-dose escalation study, dogs with *continuous access to food overnight* 5-7 hours after dosing, tolerated vorinostat reasonably well when administered up to 160 mg/kg/day *after they first received lower dose levels* (80, 100, then 120 mg/kg/day). A further increase to 200 mg/kg/day was not well tolerated, with signs of GI toxicity. Naive dogs administered 160 mg/kg/day as the initial dose developed GI toxicity.
    - No adverse effects in dogs administered at doses 20 and 60 mg/kg/day (animals were fed overnight).

- In the dose escalation portion of the study, **NOAEL was 60 mg/kg/day**.
- All animals except 1 female survived until the end of the study.
    - **No treatment-related findings, at any dose, in the surviving animals** were noted for the end points of body weight, food consumption, ophthalmologic abnormalities, electrocardiographic parameters, or blood pressure.
    - **Clinical pathology results were only observed in the high-dose female dogs**, differences were very slight, were not abnormally low or considered adverse, and were reversible. Changes included mild decreases in RBC counts, Hg, HCT, and WBC counts.
    - **GI toxicity** (characterized by clinical signs [inappetence and diarrhea] and macroscopic or microscopic findings was associated with the **high-dose regimen (160 mg/kg/day)**.
    - PK: exposure margins (ratio of dog to human vorinostat AUC values) were <1 (with humans given 400 mg/d, $AUC_{0\text{-}t\ h}$ was 1588 hcng/mL and C_{max} ~320 ng/mL)

Efficacy

- In a **case report** evaluating **adjuvant vorinostat** for splenic hemangiosarcoma in a 12 yr F Rhodesian Ridgeback-Pit Bull mix (Cohen et al.),
- SAHA (suberoylanilide hydroxamic acid, aka Vorinostat) was administered at 2.9 mg/kg/day starting 2 weeks post-splenectomy
    - Side effects were minimal over a period of 2 months, with periods of high alertness and activity and brief periods of mild lethargy.
    - The vorinostat dose was increased to 3.2 mg/kg/day 2 months after its initiation, and she had not shown any subsequent signs of decreased energy.
    - At the time of case report publication, Molly was disease-free at >1000 days post-splenectomy.

Pharmacokinetics

- In male Beagle dogs given vorinostat via the cephalic or femoral vein as a slow bolus over 30 sec at 2 mg/kg or 20 mg/kg in capsules (Sandhu et al.),
    - Vorinostat exhibited high serum clearance (54.7 +/- 12.9 mL/min/kg)
    - Vd_{ss} was small (0.6 +/- 0.2 L/kg)
    - $T_{1/2}$ was short (12 min)
    - Oral bioavailability was low (1.8%)
    - Absorption was rapid (T_{max} ≤ 1 hr)
    - Excretion after oral dosing was primarily via the renal route; 76.6% of the dose was recovered after oral dosing, with 67.5% in the urine and 9.1% in the feces

- 4-Week Repeat Dose Toxicokinetic Study in Beagle Dogs Administered SAHA (suberoylanilide hydroxamic acid, aka Vorinostat) by Oral Gavage with 2-week recovery. Plasma samples obtained on day 28 for the 15 and 40 mg/kg/day groups, and day 17 for the 100 mg/kg/day group.

TK Parameters in males and females following SAHA Administration to Dogs (Female/male))

Day	Dose		
	15 mg/kg	40 mg/kg	100 mg/kg
SAHA			
AUC (ng hr/mL)	220 ± 8.8/230 ± 60.5	381±159/512±120	522±211/571±304
Cmax (ng/mL)	87.4±6/161±16	258±181/287±91	188±88/204±110

- 26-Week Repeat Dose Toxicokinetic Study in Beagle Dogs Administered SAHA (aka Vorinostat) by Oral Gavage with 13-Week Interim Sacrifice and a 4-Week Recovery

Dogs TK Parameters for SAHA in Serum of Male and Female Dogs														
Dose (mg/kg/d)	Dose mg/m2/d	Dose ratio	Sex	Day	AUC (ng h/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation ratio	Cmax (ng/mL)	±SD	Dose Ratio	M:F Ratio	Accumulation Ratio
20	400	1	F	7	76	54.1	1			40	48	1		
			F	175	145	12.4	1		2	72	36	1		2
		1	M	7	92	99	1	1		42	76	1	1	
			M	175	249	124	1	2	3	84	87	1	1	2
60	1200	3	F	7	237	36	3			65	33	2		
			F	175	384	67	3		2	98	51	1		2
		3	M	7	250	27	3	1		73	16	2	1	
			M	175	346	117	1	1	1	131	93	2	1	2
80/10	1600/	>4	F	7	298	49	4			94	48	2		
0/125	2000/		F	175	398	53	3		1	126	25	2		2
/160	2500/	>4	M	7	221	41	2	1		67	65	2	2	
	3200		M	175	325	28	1	1	1	134	36	2	1	2

- Less than dose proportional increase in AUC and C_{max} were noted following 60 and 80/100/125/160 mg/kg.
- Clear gender differences were not observed.
- Minimal accumulation (<2) was observed on days 56,116, and 175 at all dose levels.

Sources

- Best Pet Rx[+] (https://bestpetrx.com/): as of May 4, 2023) Available in many doses; prices vary by dose ranges (there are *many* dose ranges, and only the lowest and highest are listed below):

  Dose range 0-50 mg, quantity 30 capsules, $176.50

  Dose range 675-700 mg, quantity 30 capsules, $1,069.99

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

- Stokes Pharmacy (https://www.stokespharmacy.com/veterinary-rx/for-veterinarians/): (as of May 4, 2023) Unavailable.

- Wedgewood Pharmacy (https://www.wedgewoodpharmacy.com/medications/): (as of May 4, 2023) Available in multiple capsule sizes[*] (only the lowest and highest available in quantity 30 are listed below):

  Dose 67 mg, quantity 30, $98.50

  Dose range 800 mg, quantity 30, $456.75

  **This dose or size 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

"Dose 30 mg/kg EOD appears to be associated with nausea. Dose 22 mg/kg EOD appears better tolerated. Maropitant daily appears to work well."

Doses used by many clinicians range from 15-30 mg/kg EOD, up to 30 mg/kg daily.

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Zolinza® (Vorinostat); Pharmacology Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration, NDA 021991, October 2006.

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